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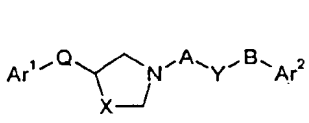
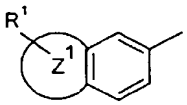
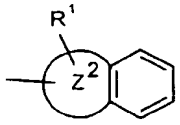


(I)



(a)



(b)

(57) Abstract: The invention relates to compounds of formula (I) wherein Ar^1 is pyridyl or phenyl, substituted by hydroxy, lower alkyl, halogen, amino, nitro, benzyloxy or lower alkoxy-lower alkoxy, or is the group (a) wherein Z^1 is a five membered heterocyclic ring, which contains one or two heteroatoms, selected from N or O; R^1 is hydrogen, hydroxy or an oxo group; Ar^2 is pyridyl or phenyl, optionally substituted by hydroxy, lower alkyl, halogen, amino, nitro, benzyloxy or lower alkoxy-lower alkoxy, or is the group (b) wherein Z^2 is a five or six membered ring, which optionally contains one or two heteroatoms, selected from N or O; and Q is -S-, -S(O)- or $-S(O)_2-$; X is a bond, -CH(OH)- or $-(CH_2)_n-$; A is a bond or $-(CHR)_m-$; R is hydrogen, halogen or hydroxy, independently from each other if m is 2 or 3; Y is $-(CR_2)_m-$, -O-, -C=C-, -C≡C-, piperidin-1-yl, pyrrolidin-1yl or C_4-C_6-cycloalkyl, which rings are optionally substituted by hydroxy; B is a bond, -O- or $-(CHR)_m$; n is 1 or 2; and m is 1 to 3 and pharmaceutically acceptable acid addition salts thereof with the exception of compounds, wherein A and B are simultaneously a bond and Y is -CHR-. The compounds may be used in the treatment of neurodegenerative diseases.

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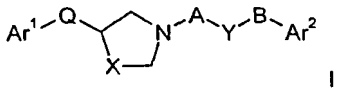
PYRROLIDINE AND PIPERIDINE DERIVATIVES AND THEIR USE FOR THE TREATMENT OF NEURODEGENERATIVE DISORDERS

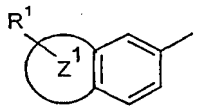
The present invention relates to compounds of the general formula



I

wherein

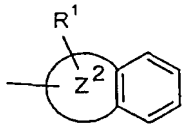
Ar^1 is pyridyl or phenyl, substituted by hydroxy, lower alkyl, halogen, amino, nitro, benzyloxy or lower alkoxy-lower alkoxy, or is the group



wherein Z^1 is a five membered heterocyclic ring, which contains one or two heteroatoms, selected from N or O;

R^1 is hydrogen, hydroxy or an oxo group;

Ar^2 is pyridyl or phenyl, optionally substituted by hydroxy, lower alkyl, halogen, amino, nitro, benzyloxy or lower alkoxy-lower alkoxy, or is the group



wherein Z^2 is a five or six membered ring, which optionally contains one or two heteroatoms, selected from N or O; and

Q is –S-, -S(O)- or $-S(O)_2$-;

X is a bond, -CH(OH)- or $-(CH_2)_n$-;

A is a bond or $-(CHR)_m$-;

R is hydrogen, halogen or hydroxy, independently from each other if m is 2 or 3;

Y		is $-(CR_2)_m-$, -O-, -C=C-, -C≡C-, piperidin-1-yl, pyrrolidin-1-yl or C_4-C_6-cycloalkyl, which rings are optionally substituted by hydroxy;
B		is a bond, -O- or $-(CHR)_m$;
n		is 1 or 2; and
m		is 1, 2 or 3;

and to pharmaceutically acceptable acid addition salts thereof.

Excluded from the scope of formula I are those compounds, wherein A and B are simultaneously a bond and Y is –CHR-. These compounds have been described in EP 160 436, useful as antiarrhytmic agents.

The present invention embraces racemic mixtures and all their corresponding enantiomers.

The compounds of formula I and their salts are distinguished by valuable therapeutic properties. Compounds of the present invention are NMDA (N-methyl-D-aspartate)-receptor subtype selective blockers, which have a key function in modulating neuronal activity and plasticity which makes them key players in mediating processes underlying development of CNS as well as learning and memory formation.

Under pathological conditions of acute and chronic forms of neurodegeneration overactivation of NMDA receptors is a key event for triggering neuronal cell death. NMDA receptors are composed of members from two subunit families, namely NR-1 (8 different splice variants) and NR-2 (A to D) originating from different genes. Members from the two subunit families show a distinct distribution in different brain areas. Heteromeric combinations of NR-1 members with different NR-2 subunits result in NMDA receptors displaying different pharmaceutical properties. Possible therapeutic indications for NMDA receptor subtype specific blockers include acute forms of neurodegeneration caused, e.g., by stroke and brain trauma, and chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis) and neurodegeneration associated with bacterial or viral infections, and, in addition, chronic and acute pain.

Objects of the invention are the compounds of formula I and pharmaceutically acceptable acid addition salts thereof, the preparation of the compounds of formula I and salts thereof, medicaments containing a compound of formula I or a pharmaceutically acceptable acid addition salt thereof, the manufacture of such medicaments and the use of the compounds of formula I and their pharmaceutically acceptable salts in the control or

prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier, and, respectively, for the manufacture of corresponding medicaments.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1 to 7 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl and the like. Preferred are groups from 1 to 4 carbon atoms.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

The term "lower alkoxy" denotes a group wherein the alkyl residue is as defined above.

A "five membered heterocyclic ring, which contains one or two heteroatoms, selected from N or O" denotes, for example, oxazolyl, isoxazolyl, furyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolidinyl, imidazolinyl, pyrazolyl, pyrazolidinyl or pyrazolinyl.

A "five or six membered ring, which optionally contains one or two heteroatoms, selected from N or O" are, for example; cyclopentyl, cyclohexyl, oxazolyl, isoxazolyl, furyl, pyrrolyl, pyrrolidinyl, pyrrolinyl, imidazolyl, imidazolidinyl, imidazolinyl, pyrazolyl, pyrazolidinyl, pyrazolinyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, piperidyl, piperazinyl or morpholinyl.

The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

Preferred compounds of formula I in the scope of the present invention are those, wherein Ar^1 is phenyl, substituted by hydroxy, Q is –S-, Ar^2 is phenyl and X is $–CH_2$. These are the following compounds:

(S)-4-[1-(4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(RS)-4-[1-(4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(R)-4-[1-(4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(2R, 3S) or (2S, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(2S, 3S) or (2R, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(RS)-4-[1-(3-phenyl-propyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(3RS, 3RS) and (3RS, 3SR)-4-[1-(3-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-

phenol,
(2S, 3R) or (2R, 3R)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(2RS,3S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol or
(2RS,3R)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Compounds of the present invention, in which Ar^1 is phenyl, substituted by hydroxy, Q is –S(O)-, Ar^2 is phenyl and X is $–CH_2$- are further preferred, for example the following compound:

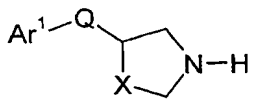
(3RS, S-oxide RS) and (3RS, S-oxide SR)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol,
(2R,3R, S-oxide R)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol,
(2S,3S, S-oxide R)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol,
(2R,3S, S-oxide R)-4-[1-(2-fuoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol or
(3S, S-oxide S) or (3S, S-oxide R)-4-[1-(2,2-difluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol.

Further preferred are compounds, in which Ar^1 is phenyl, substituted by hydroxy, Q is $–S(O)_2$-, Ar^2 is indanyl or phenyl, optionally substituted by methyl and X is $–CH_2$- or –CH(OH)-, for example the following compounds:

(S)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(RS)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(2R, 3S) and (2S, 3S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(3RS, cis) and (3RS, trans)-4-[1-(3-benzyl-cyclobutyl)-pyrrolidine-3-sulfonyl]-phenol,
(3RS, cis)- 4-[1-(4-phenyl-cyclohexyl)-pyrrolidine-3-sulfonyl]-phenol,
(3RS,4RS)-4-(4-hydroxy-benzenesulfonyl)-1-(4-phenyl-butyl)-pyrrolidin-3-ol,
(RS)-4-[1-(4-m-tolyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(RS)-4-[1-(3-phenyl-propyl)-pyrrolidine-3-sulfonyl]-phenol,
(R)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(RS)-4-[1-(1-phenyl-piperidin-4-yl)-pyrrolidine-3-sulfonyl]-phenol or
(2R, 3S) or (2S, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol.

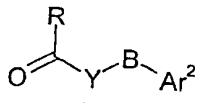
The afore-mentioned compounds of formula I can be manufactured in accordance with the invention by

a) reacting a secondary amine of formula



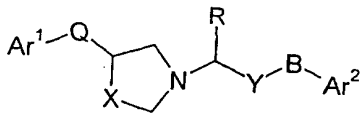
II

with an aldehyde or ketone of formula



III

to a compound of formula

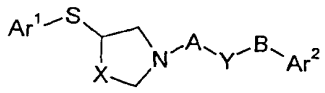


I-1

wherein Ar^1, Ar^2, Q, X, Y, R and B have the significances given above,

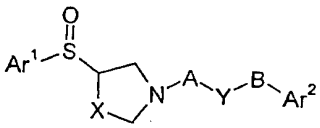
or

b) oxydizing a compound of formula



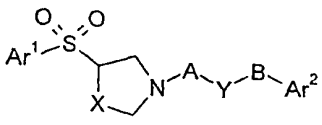
I-2

to a compound of formula



I-3

and /or to a compound of formula

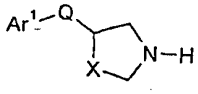


I-4

wherein Ar^1, Ar^2, X, A, Y and B have the significances given above,

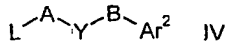
or

c) reacting a secondary amine of formula



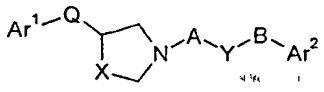
II

with a compound of formula



IV

to give a compound of formula

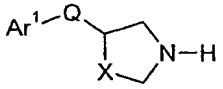


I

wherein L is a leaving group, such as Cl, Br or p-toluenesulfonate and Ar^1, Ar^2, Q, X, A, Y and B have the significances given above,

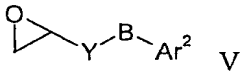
or

d) reacting a secondary amine of formula



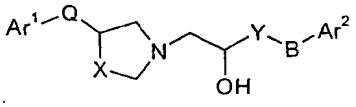
II

with a compound of formula



V

to give a compound of formula

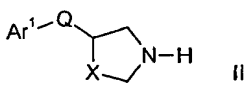


I-5

wherein Ar^1, Ar^2, Q, X, Y and B have the significances given above,

or

e) reacting a secondary amine of formula

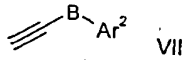


II

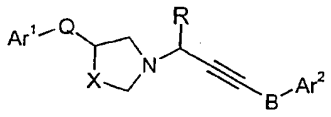
with an aldehyde of formula

VI

and with an alkyne of formula


VII

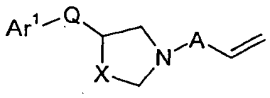
to give a compound of formula


I-6

wherein Ar^1, Ar^2, Q, X, R and B have the significances given above ,

or

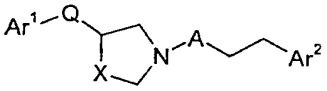
f) reacting a compound of formula


VIII

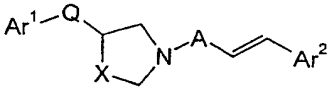
with a compound of formula

Ar^2hal

to give a comound of formula


I-7

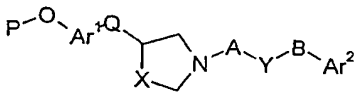
or


I-8

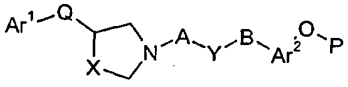
wherein Ar^1, Ar^2, Q, X and A have the significances given above ,

or

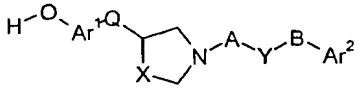
g) cleaving off a O-protecting group of compounds of formula


X

or

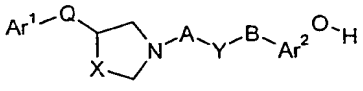

XI

to obtain a compound of formula



I-9

or

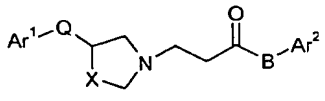


I-10

wherein Ar^1, Ar^2, Q, X, A, Y and B have the significances given above and P is a O-protecting group, for example benzyl or a methoxymethyl group,

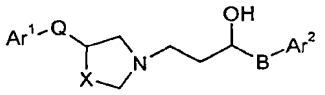
or

h) reducing a compound of formula



XII

to a compound of formula

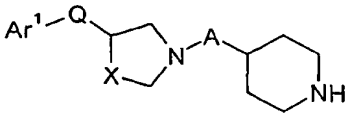


I-11

wherein Ar^1, Ar^2, Q, X and B have the significances given above;

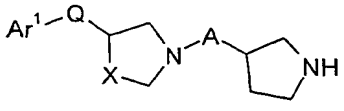
or

i) reacting a compound of formula



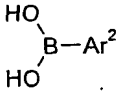
XIV-2

or



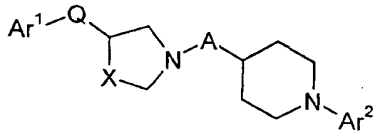
XIV-1

with a compound of formula

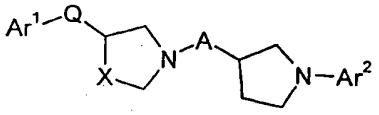


XV

to obtain a compound of formula



or



I-13 I-12

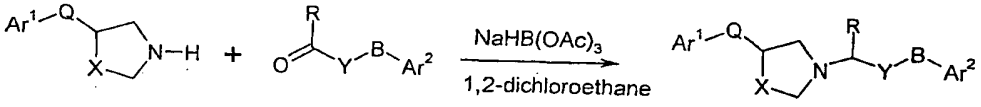
wherein Ar^1, Ar^2, Q, X, A and B have the significances given above;

and

if desired, modifying one or more substituents within the definitions given above, or if desired, converting the compound of formula I obtained into a pharmaceutically acceptable salt.

In the following the preparation of compounds of formula I are described in more detail:

Scheme 1

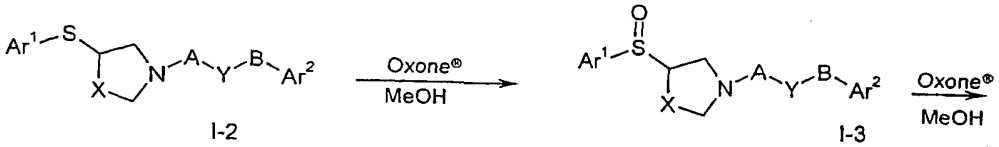


II III I-1

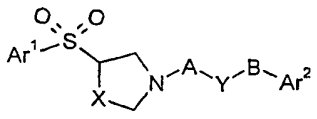
wherein Ar^1, Ar^2, Q, Y, R and B have the significances given above.

Compounds of formula I (A is –CHR-) can be prepared by reacting a secondary amine of formula II with an aldehyde or ketone of formula III in the presence of a reducing agent like $NaHB(OAc)_3$ in conventional manner.

Scheme 2



I-2 I-3



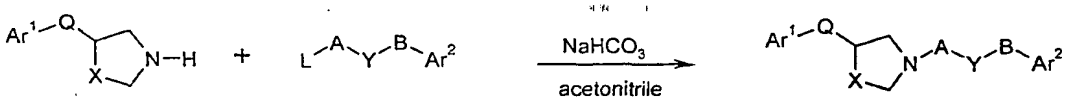
I-4

wherein Ar^1, Ar^2, X, A, Y, R and B have the significances given above.

The compound of formula I-4 (Q is $-SO_2-$) can be prepared by oxidation of

compounds of formula I-3 (Q is -SO-), which itself can be prepared by oxidation of compounds of formula I-2 (Q is -S-), using oxone® as oxidative agent.

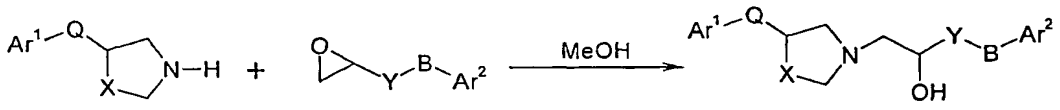
Scheme 3



II IV I

Compounds of formula I can be prepared by reacting an amine of formula II with an electrophile compound of formula IV, wherein L is a leaving group like Cl, Br or p-toluenesulfonate and the remaining substituents are described above.

Scheme 4

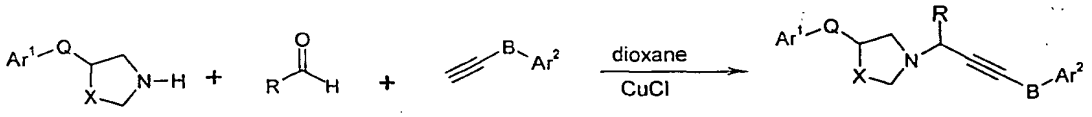


II V I-5

wherein Ar^1, Ar^2, Q, X, Y and B have the significances given above.

Compounds of formula I-5, wherein A is $-CH_2-CH(OH)-$ can be prepared by reacting of an amine of formula II with an epoxide of formula V in conventional manner.

Scheme 5

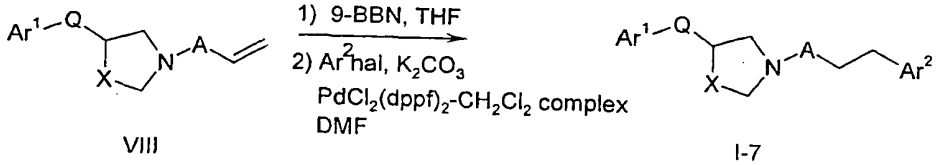


II VI VII I-6

wherein Ar^1, Ar^2, Q, X, R and B have the significances given above.

Compounds of formula I-6, whereinA is –CHR- and Y is -C≡C- can be prepared under Mannich conditions by reacting an amine of compound of formula II with an aldehyde of formula VI and an alkyne of formula VII.

Scheme 6

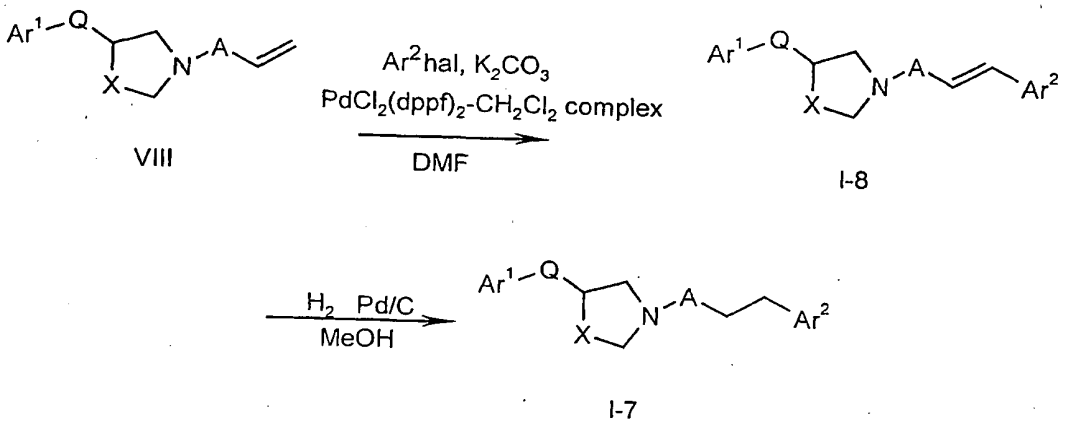


VIII I-7

wherein Ar^1, Ar^2, Q, X and A have the significances given above.

Compounds of formula I-7, wherein Y is $-CH_2$ and B is $-CH_2-$ can be prepared under Suzuki conditions by reacting an alkene of formula VIII with Ar^2hal, wherein hal is an halogene like Br or I.

Scheme 7



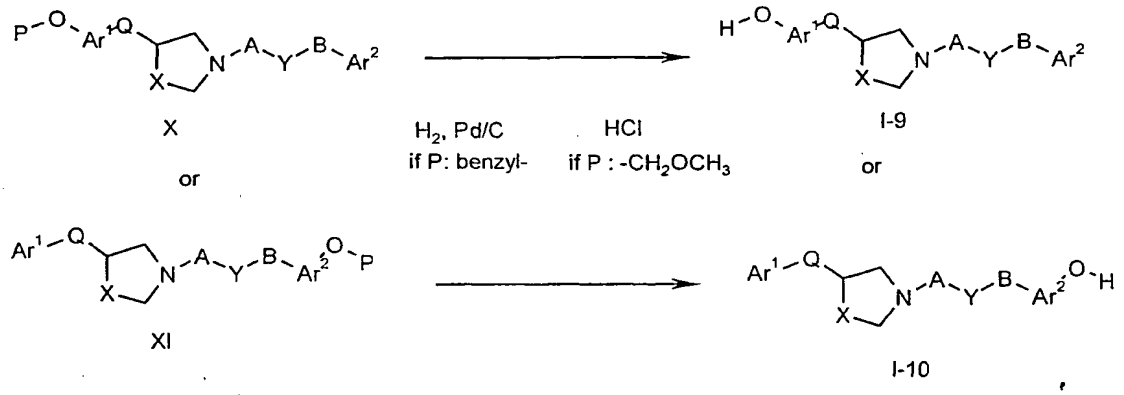
VIII I-8

I-7

wherein Ar^1, Ar^2, Q, X and A have the significances given above.

Alternatively, compounds of formula I-7, wherein Y is $-CH_2-$ and -B- is $-CH_2-$ can be prepared in two steps under Heck conditions. Alkene compounds of formula VIII can react with Ar^2hal, wherein hal is an halogen like Br or I to provide an alkene derivative of formula I-8 which can be subsequently hydrogenated to obtain compounds of formula I-7.

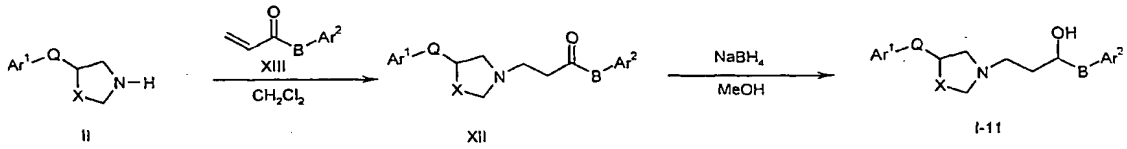
Scheme 8



wherein Ar^1, Ar^2, Q, X, A, Y and B have the significances given above and P is a O-protecting group, which may be, for example benzyl or methoxymethyl.

Compounds of formula I-9 or of compounds of formula I-10 can be prepared by cleaving off an O-protecting group of compounds of formulas X or XI. H_2-Pd/C have been used to cleave a benzylether and acidic conditions have been used to cleave a methoxymethyl ether.

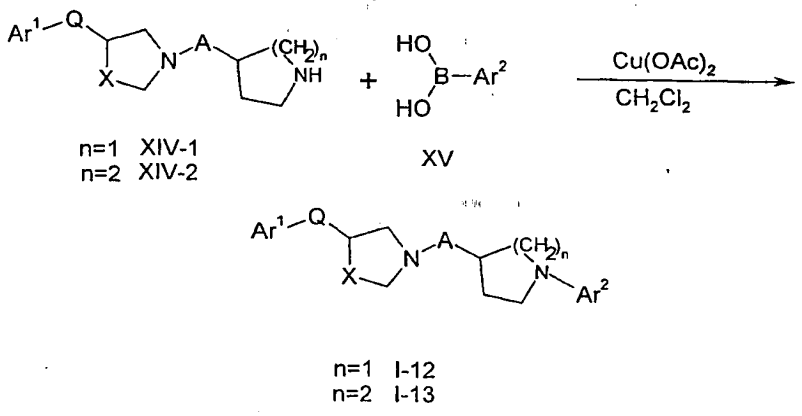
Scheme 9



wherein Ar^1, Ar^2, Q, X and B have the significances given above.

Compounds of formula I-11, wherein A is $-CH_2-$ and Y is $-CH_2CH(OH)-$ can be prepared by reducing a ketone of formula XII, which itself can be prepared by reacting an amine of formula II with a Michael acceptor of formula XIII.

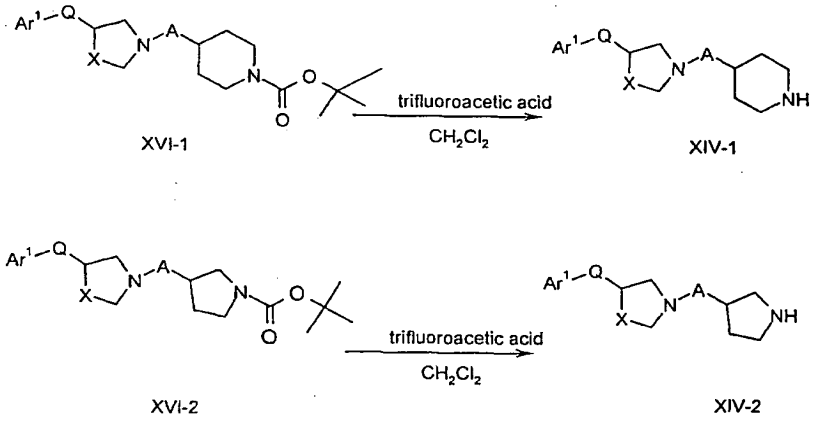
Scheme 10



wherein Ar^1, Ar^2, Q, X, A and B have the significances given above.

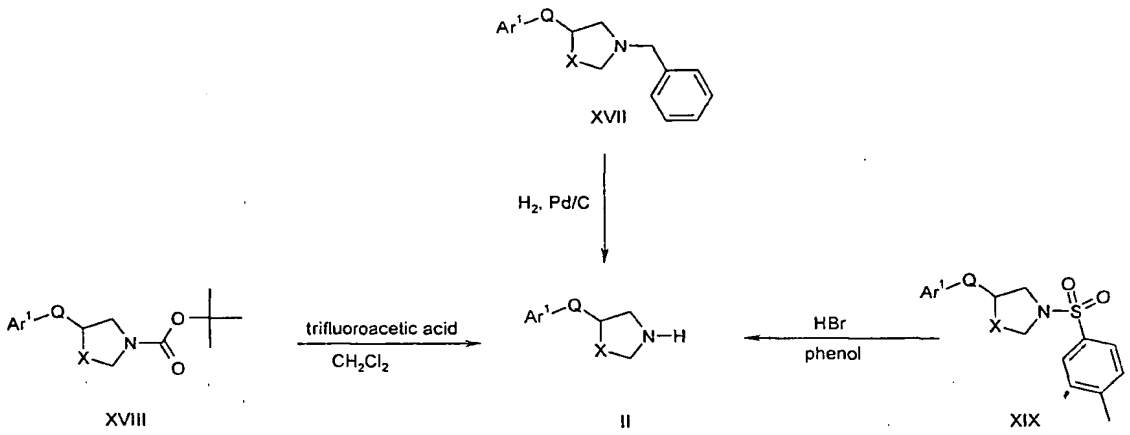
Compounds of formula I-12 and I-13 can be prepared by reacting of an amine compound of formula XIV-1 or XIV-2 with boronic acid of formula XV.

Scheme 11



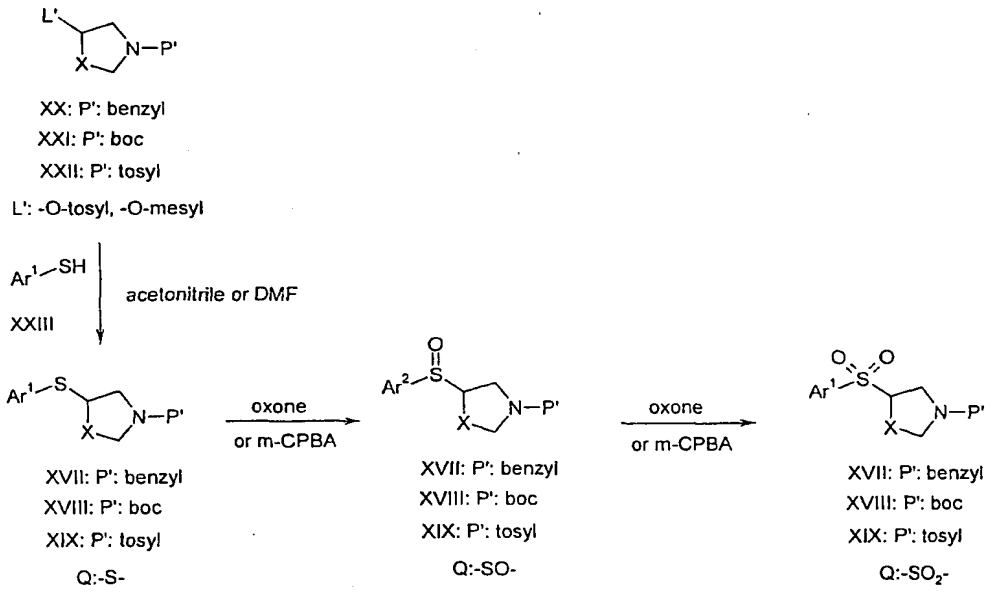
A compound of formula XIV-1 or of XIV-2 can be prepared by treating the boc-protected amine compound of formula XVI-1 or XVI-2 with an acid, for example with trifluoroacetic acid.

Scheme 12



A compound of formula II can be prepared by hydrogenolysis of the benzylated amine of formula XVII, or by acidic hydrolysis of either the boc-protected amine compound of formula XVIII or the tosyl-protected amine compound of formula XIX.

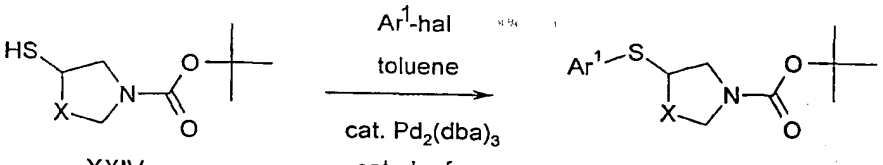
Scheme 13



Compounds of formulas XVII, XVIII and XIX, wherein Q is $-SO_2-$, can be prepared by oxidation of compounds, respectively XVII, XVIII and XIX, wherein Q is -SO-, which themselves can be prepared by oxidation of compounds, respectively XVII, XVIII and XIX, wherein Q is -S-, using oxone or m-CPBA as oxidative agent.

Compounds of formulas XVII, XVIII and XIX , wherein Q is -S- can be prepared by reaction of a thiol of formula XXIII with respectively electrophiles of formulas XX, XXI and XXII, wherein L' is a leaving group, such as p-toluenesulfonate or mesylate.

Scheme 14



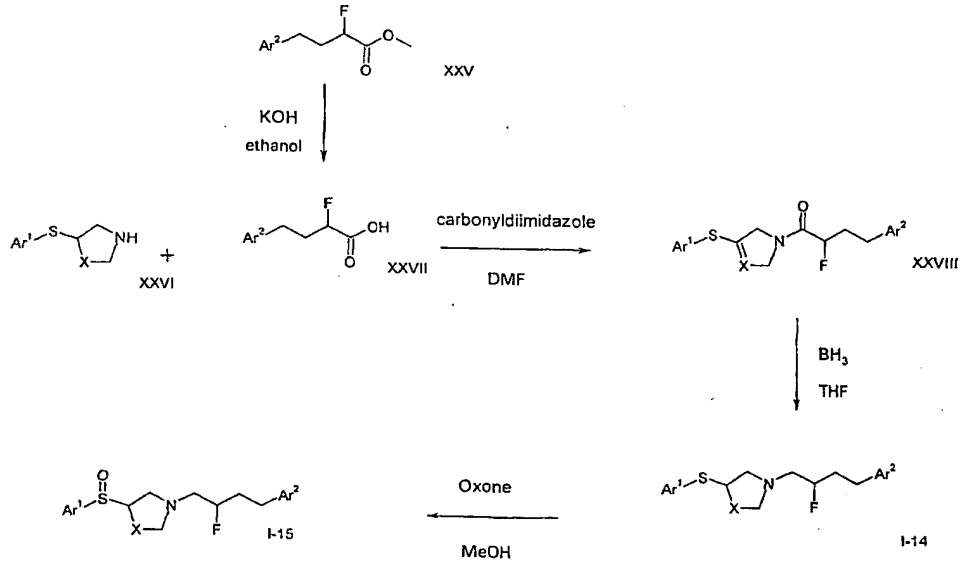
Alternatively, compounds of formula XVIII, wherein Q is -S- can be prepared by reacting a thiol of formula XXIV with Ar^1-hal in the presence of a catalytic amount of $Pd_2(dba)_3$ and DPPF.

$Pd_2(dba)_3$ is tris(dibenzylideneacetone)dipalladium and

dppf is 1,1'-bis(diphenylphosphino)ferrocene.

Scheme 15

Synthesis of monofluoro sulfoxides

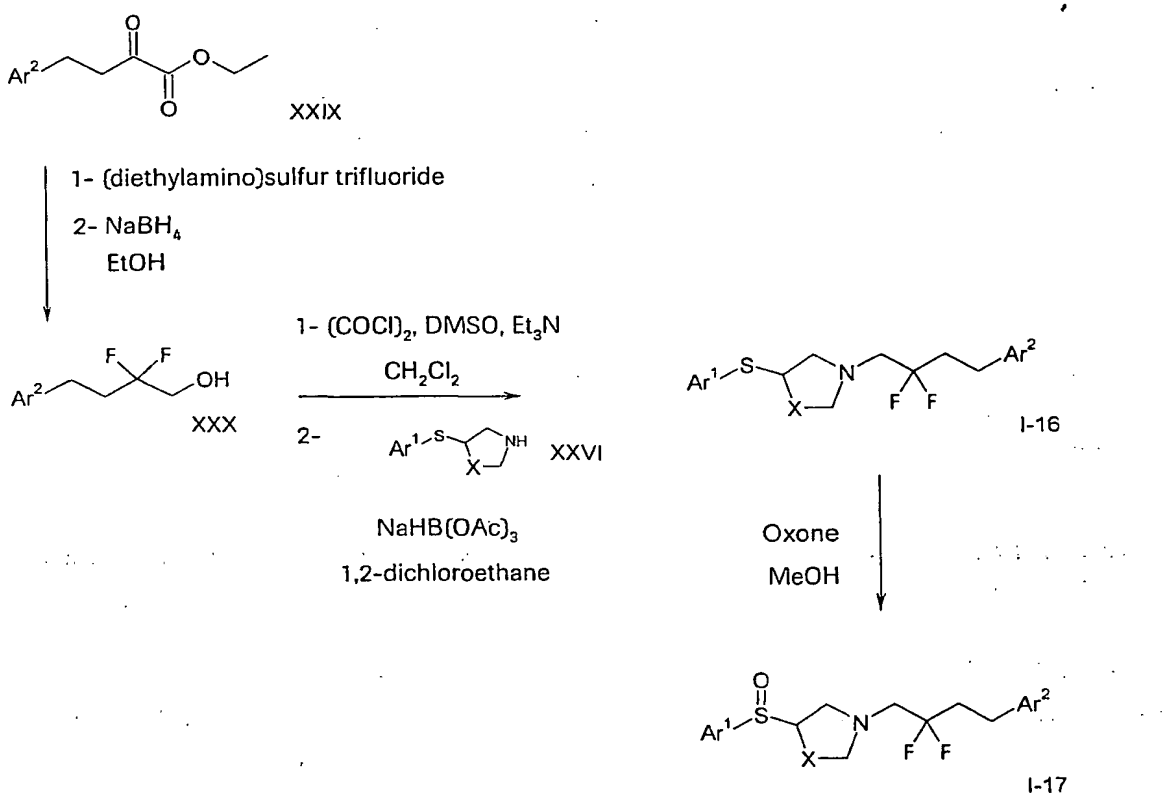


The monofluoro sulfoxides are obtained by oxidation of the corresponding sulfides with oxone. The sulfides are prepared by reduction of the amides with borane

dimethylsulfide complexe. The amides are accessible by coupling the racemic monofluoroacid with the R or S configurated pyrrolidines in the presence of an activating agent like carbonyldimidazole. The racemic acid is prepared by saponification of the corresponding racemic methyl ester. This methyl ester as well as the R or S configurated pyrrolidines have been described in more detail in the working examples.

Scheme 16

Synthesis of difluoro sulfoxides:



The difluoro sulfoxides are obtained by oxidation of the corresponding sulfides with oxone. The sulfides are prepared from the achiral difluoro alcohol after a Swern oxidation and reductive amination in the presence of a R or S configurated pyrrolidine and sodium triacetoxyborohydride as reducing agent. The alcohol is obtained from the commercially available ethyl 2-oxo 4-phenylbutyrate after treatment with DAST ((diethylamino)sulfur trifluoride) and reduction with sodium borohydride.

The starting materials of formulas III, IV, V, VI, VII, XIII, XV, XX, XXI, XXII, XXIII, XXVI and XXIX are commercial products or can be prepared according to methods known per se.

Pharmaceutically acceptable salts can be manufactured according to methods which are known per se and familiar to any person skilled in the art. The acid addition salts of compounds of formula I are especially well suited for pharmaceutical use.

In schemes 1 – 10 and 15 and 16 are described processes for preparation of compounds of formula I, starting from known compounds, from commercial products or from compounds, which can be prepared in conventional manner. In schemes 11 – 14 are described processes for the preparation of intermediates.

The preparation of compounds of formula I are described in more detail in working examples 1 - 69.

As mentioned earlier, the compounds of formula I and their pharmaceutically usable acid addition salts possess valuable pharmacodynamic properties. They are NMDA-receptor subtype selective blockers, which have a key function in modulating neuronal activity and plasticity which makes them key players in mediating processes underlying development of CNS as well as learning and memory formation.

The compounds were investigated in accordance with the test given hereinafter.

Test method

3H-Ro 25-6981 binding (Ro 25-6981 is [R-(R*,S*)]-a-(4-hydroxy-phenyl)-b-methyl-4-(phenyl-methyl)-1-piperidine propanol)

Male Füllinsdorf albino rats weighing between 150-200 g were used. Membranes were prepared by homogenization of the whole brain minus cerebellum and medulla oblongata with a Polytron (10.000 rpm, 30 seconds), in 25 volumes of a cold Tris-HCl 50 mM, EDTA 10 mM, pH 7.1 buffer. The homogenate was centrifuged at 48.000 g for 10 minutes at 4 °C. The pellet was resuspended using the Polytron in the same volume of buffer and the homogenate was incubated at 37 °C for 10 minutes. After centrifugation the pellet was homogenized in the same buffer and frozen at –80 °C for at least 16 hours but not more than 10 days. For the binding assay the homogenate was thawed at 37 °C, centrifuged and the pellet was washed three times as above in a Tris-HCl 5 mM, pH 7.4 cold buffer. The final pellet was resuspended in the same buffer and used at a final concentration of 200 mg of protein/ml.

3H-Ro 25-6981 binding experiments were performed using a Tris-HCl 50 mM, pH 7.4 buffer. For displacement experiments 5 nM of 3H-Ro 25-6981 were used and non specific binding was measured using 10 mM of tetrahydroisoquinoline and usually it accounts for 10% of the total. The incubation time was 2 hours at 4°C and the assay was stopped by filtration on Whatmann GF/B glass fiber filters (Unifilter-96, Packard, Zürich, Switzerland). The filters were washed 5 times with cold buffer. The radioactivity on the filter was counted on a Packard Top-count microplate scintillation counter after addition of 40 mL of microscint 40 (Canberra Packard S.A., Zürich, Switzerland).

The effects of compounds were measured using a minimum of 8 concentrations and repeated at least once. The pooled normalized values were analyzed using a non-linear regression calculation program which provide IC_{50} with their relative upper and lower 95% confidence limits (RS1, BBN, USA).

The IC_{50} (μM) of preferred compounds tested in accordance with the above mentioned methods are in the range of about 0.009 – 0.100.

Examples of some IC_{50} values of preferred compounds are given in the table below:

Example	IC_{50} (μM)
2	0.009
3	0.02
35	0.029
43	0.031
4	0.04
6	0.059
62	0.06
68	0.077
16	0.08

The compounds of formula I and their salts, as herein described, can be incorporated into standard pharmaceutical dosage forms, for example, for oral or parenteral application

with the usual pharmaceutical adjuvant materials, for example, organic or inorganic inert carrier materials, such as, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkylene-glycols and the like. The pharmaceutical preparations can be employed in a solid form, for example, as tablets, suppositories, capsules, or in liquid form, for example, as solutions, suspensions or emulsions. Pharmaceutical adjuvant materials can be added and include preservatives stabilizers, wetting or emulsifying agents, salts to change the osmotic pressure or to act as buffers. The pharmaceutical preparations can also contain other therapeutically active substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In the case of oral administration the dosage lies in the range of about 0.1 mg per dosage to about 1000 mg per day of a compound of general formula I although the upper limit can also be exceeded when this is shown to be indicated.

The following examples illustrate the present invention in more detail. However, they are not intended to limit its scope in any manner. All temperatures are given in degree celsius.

Example 1

(RS)-4-[1-(4-Phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol hydrochloride

(RS)-4-(Pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt (0.22 g, 0.65 mmol), 4-phenyl-butyraldehyde (0.096 g, 0.65 mmol), triethylamine (0.090 ml, 0.65 mmol), and sodium triacetoxyborohydride (0.2 g, 0.97 mmol) were suspended in 1,2-dichloroethane (4 ml). After 3 hours stirring at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$ (10 ml). The aqueous phase was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 19:1) to provide a white solid which was suspensed in MeOH. HCl-Et_2O was added to provide (RS)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol hydrochloride (0.180 g, 70%) as a white solid, m.p. 121-124°C and MS: m/e = 360.3 ($M+H^+$).

4-Phenyl-butyraldehyde is a known compound and has been prepared as described in the following reference: S. M. Moosavi; R. S. Beddoes; C. I. F. Watt; J. Chem. Soc. Perkin Trans. 2, 8, 1997, 1585-1596.

Following the general method of example 1 the compounds of example 2 to example 17 were prepared.

Example 2

(S)-4-[1-(4-Phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol

The title compound, MS: m/e = 328.3 ($M+H^+$) and $[\alpha]_D^{20}$ = -6.26 ° (c = 0.61, chloroform) was prepared from (S)-4-(pyrrolidin-3-yl-sulfanyl)-phenol hydrobromide and 4-phenyl-butyraldehyde.

Example 3

(R)-4-[1-(4-Phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol

The title compound, MS: m/e = 328.3 ($M+H^+$) and $[\alpha]_D^{20}$ = +10.15 ° (c = 0.56, chloroform) was prepared from (R)- 4-(pyrrolidin-3-yl-sulfanyl)-phenol trifluoroacetic acid salt and 4-phenyl-butyraldehyde.

Example 4

(3RS, cis) and (3RS, trans)-4-[1-(3-Benzyl-cyclobutyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 372.3 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and 3-benzyl-cyclobutanone.

Example 5

(RS)-4-[1-(3-Phenyl-propyl)-pyrrolidin-3-yl-sulfanyl]-phenol hydrochloride

The title compound, MS: m/e = 314.3 ($M+H^+$) was prepared from (RS)-4-(pyrrolidin-3-yl-sulfanyl)-phenol hydrobromide and 3-phenylpropionaldehyde.

Example 6

(3RS, cis)- 4-[1-(4-Phenyl-cyclohexyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 386.3 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid and 4-phenylcyclohexanone.

Example 7

(3RS, trans)-4-[1-(4-Phenyl-cyclohexyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 386.3 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid and 4-phenylcyclohexanone.

Example 8

(RS)-4-[1-(3-Phenyl-propyl)-piperidin-3-yl-sulfanyl]-phenol

The title compound, MS: m/e = 328.3 ($M+H^+$) was prepared from (RS)-4-(piperidin-3-yl-sulfanyl)-phenol hydrobromide and 3-phenylpropionaldehyde.

Example 9

(RS)- 5-[1-(4-Phenyl-butyl)-pyrrolidine-3-sulfonyl]-1H-indazole

The title compound, MS: m/e = 384.2($M+H^+$) was prepared from (RS)-5-(pyrrolidine-3-sulfonyl)-1H-indazole trifluoroacetic acid and 4-phenyl-butyraldehyde.

Example 10

(RS)-4-[1-(2-Benzyloxy-ethyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 362.2 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and benzyloxyacetaldehyde.

Example 11

4-[1-(4-Phenyl-butyl)-azetidine-3-sulfonyl]-phenol hydrochloride

The title compound, MS: m/e = 346.3 ($M+H^+$) was prepared from 4-(azetidine-3-sulfonyl)-phenol and 4-phenyl-butyraldehyde.

Example 12

(RS)-3-[1-(3-Phenyl-propyl)-pyrrolidin-3-yl-sulfanyl]-phenol

The title compound, MS: m/e = 314.3 ($M+H^+$) was prepared from (RS)-3-(pyrrolidin-3-yl-sulfanyl)-phenol hydrochloride and 3-phenylpropionaldehyde.

Example 13

(RS)-6-[1-(4-Phenyl-butyl)-pyrrolidine-3-sulfonyl]-3H-benzooxazol-2-one

The title compound, MS: m/e = 401.4 ($M+H^+$) was prepared from (RS)-6-(pyrrolidine-3-sulfonyl)-3H-benzooxazol-2-one trifluoroacetic acid and 4-phenyl-butyraldehyde.

Example 14

(RS)-5-[1-(4-Phenyl-butyl)-pyrrolidine-3-sulfonyl]-1,3-dihydro-indol-2-one

The title compound, MS: m/e = 399.4 ($M+H^+$) was prepared from (RS)-5-(pyrrolidine-3-sulfonyl)-1,3-dihydro-indol-2-one trifluoroacetic acid and 4-phenyl-butyraldehyde.

Example 15

(RS)-4-[1-(4-Phenyl-butyl)-piperidin-3-yl-sulfanyl]-phenol

The title compound, MS: m/e = 342.3 ($M+H^+$) was prepared from (RS)-4-(piperidin-3-yl-sulfanyl)-phenol hydrobromide and 4-phenyl-butyraldehyde.

Example 16

(3RS,4RS)-4-(4-Hydroxy-benzenesulfonyl)-1-(4-phenyl-butyl)-pyrrolidin-3-ol

The title compound, MS: m/e = 376.3 ($M+H^+$) was prepared from (3RS,4RS)-4-(4-hydroxy-benzenesulfonyl)-pyrrolidin-3-ol and 4-phenyl-butyraldehyde.

Example 17

(RS)-4-[1-(4-Phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol hydrochloride

The title compound, MS: m/e = 328.2 ($M+H^+$) was prepared from (RS)-4-(pyrrolidin-3-yl-sulfanyl)-phenol hydrobromide and 4-phenyl-butyraldehyde.

Example 18

(3RS, S-oxide RS) and (3RS, S-oxide SR)-4-[1-(4-Phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol hydrochloride

(RS)-4-[1-(4-Phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol (0.15 g, 0.46 mmol) was dissolved in MeOH (4 ml), cooled to 0 °C and treated with oxone (0.28 g, 0.46 mmol). After 1 hour stirring at 0 °C, the reaction mixture was quenched with saturated $NaHCO_3$ (15 ml). The aqueous phase was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (ethyl acetate then ethyl acetate-MeOH, 95:5 then 9:1) to provide an oil which was suspensed in MeOH. HCl-Et_2O was added to provide (3RS, S-oxide RS) and (3RS, S-oxide SR)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol hydrochloride (0.04 g, 23%) as a foam, MS: m/e = 344.2 ($M+H^+$).

Following the general method of example 18 the compounds of example 19 to example 30 were prepared.

Example 19

(S)-4-[1-(4-Phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 360.3 ($M+H^+$) and $[\alpha]_D^{20}$ = + 2.62 ° (c = 0.534, chloroform) was prepared from (S)-4-[1-(4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 20

(R)-4-[1-(4-Phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol hydrochloride

The title compound, MS: m/e = 360.3 ($M+H^+$) was prepared from (R)-4-[1-(4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 21

(RS)-4-[1-(3-Phenyl-propyl)-pyrrolidine-3-sulfonyl]-phenol hydrochloride

The title compound, MS: m/e = 346.4 ($M+H^+$) was prepared from (RS)- 4-[1-(3-phenyl-propyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 22

(2R, 3S) or (2S, 3S)-4-[1-(2-Hydroxy-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 376.4 ($M+H^+$) was prepared from (2R, 3S) or (2S, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 23

(2S, 3S) or (2R, 3S)- 4-[1-(2-Hydroxy-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 376.4 ($M+H^+$) was prepared from (2S, 3S) or (2R, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 24

(2R, 3R) or (2S, 3R)-4-[1-(2-Hydroxy-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 376.3 ($M+H^+$) was prepared from (2R, 3R) or (2S, 3R)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 25

(2S, 3R) or (2R, 3R)-4-[1-(2-Hydroxy-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 376.4 ($M+H^+$) was prepared from (2S, 3R) or (2R, 3R)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 26

(3RS, S-oxide RS) and (3RS, S-oxide SR)-4-[1-(3-Phenyl-propyl)-piperidine-3-sulfinyl]-phenol hydrochloride

The title compound, MS: m/e = 344.4 ($M+H^+$) was prepared from (RS)-4-[1-(3-phenyl-propyl)-piperidin-3-yl-sulfanyl]-phenol.

Example 27

(RS)-4-[1-(3-Phenyl-propyl)-piperidine-3-sulfonyl]-phenol hydrochloride

The title compound, MS: m/e = 360.3 ($M+H^+$) was prepared from (RS)-4-[1-(3-phenyl-propyl)-piperidin-3-yl-sulfanyl]-phenol.

Example 28

(RS)-4-[1-(4-Phenyl-butyl)-piperidine-3-sulfonyl]-phenol hydrochloride

The title compound, MS: m/e = 374.4 ($M+H^+$) was prepared from (RS)-4-[1-(4-phenyl-butyl)-piperidin-3-yl-sulfanyl]-phenol.

Example 29

(3RS, S-oxide RS) and (3RS, S-oxide SR)-4-[1-(3-Phenyl-propyl)-pyrrolidine-3-sulfinyl]-phenol hydrochloride

The title compound, MS: m/e = 330.4 ($M+H^+$) was prepared from (RS)-4-[1-(3-phenyl-propyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 30

(3RS, 3RS) and (3RS, 3SR)-4-[1-(3-Hydroxy-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 376.4 ($M+H^+$) was prepared from (3RS, 3RS) and (3RS, 3SR)-4-[1-(3-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

Example 31

(RS)-4-[1-(3-Phenoxy-propyl)-pyrrolidine-3-sulfonyl]-phenol(RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt (0.2 g, 0.585 mmol), 3-phenoxypropylbromide (0.137g, 0.64 mmol), and $NaHCO_3$ (0.1 g, 1.23 mmol) were suspended in acetonitrile (1.5 ml). After 24 hours stirring at 55 °C, the reaction mixture was cooled to room temperature and quenched with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 times). The combined organic phases were washed with H_2O, dried over Na_2SO_4 and the solvent was evaporated. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 19:1) to provide (RS)-4-[1-(3-phenoxy-propyl)-pyrrolidine-3-sulfonyl]-phenol (0.16 g, 75%) as a white foam, MS: m/e = 362.2 ($M+H^+$).

Following the general method of example 31 the compounds of example 32 to example 38 were prepared.

Example 32

(RS)-4-[1-(2-Indan-2-yl-ethyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 372.3 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and toluene-4-sulfonic acid 2-indan-2-yl-ethyl ester.

Toluene-4-sulfonic acid 2-indan-2-yl-ethyl ester is a known compound and has been prepared as described in US 3,984,407.

Example 33

(RS)-2-{2-[3-(4-Hydroxy-benzenesulfonyl)-pyrrolidin-1-yl]-ethyl}-indan-2-ol hydrochloride

The title compound, MS: m/e = 388.2 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and toluene-4-sulfonic acid 2-(2-hydroxy-indan-2-yl)-ethyl ester.

Example 34

(RS)-4-[1-(5-Phenyl-pentyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 374.4 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and (5-bromo-pentyl)-benzene.

(5-Bromo-pentyl)-benzene is a known compound and has been prepared as described in the following reference: J. Thomas; W. Marlow; J. Med. Chem.; 6; 1963; 107-111.

Example 35

(2R, 3S) and (2S, 3S)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 378.3 ($M+H^+$) was prepared from (S)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and (RS)-toluene-4-sulfonic acid 2-fluoro-4-phenyl-butyl ester.

Example 36

(2RS, 3RS) and (2RS, 3SR)-2-{2-[3-(4-Hydroxy-benzenesulfonyl)-pyrrolidin-1-yl]-ethyl}-1,2,3,4-tetrahydro-naphthalen-2-ol

The title compound, MS: m/e = 402.4 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and (RS)-2-(2-bromo-ethyl)-1,2,3,4-tetrahydro-naphthalen-2-ol.

Example 37

(RS)-4-[1-(4-Phenyl-but-3-ynyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 355.1 (M^+) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and toluene-4-sulfonic acid 4-phenyl-but-3-ynyl ester.

Example 38

(RS)-4-{1-[2-(1,3-Dihydro-isoindol-2-yl)-ethyl]-pyrrolidine-3-sulfonyl)-phenol hydrochloride

The title compound, MS: m/e = 373.3 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and 2-(2-chloro-ethyl)-2,3-dihydro-1H-isoindole.

2-(2-Chloro-ethyl)-2,3-dihydro-1H-isoindole is a known compound and has been prepared as described in the following reference: G. Shoeb; J. Pharm. Sci.; 51; 1962; 469-471.

Example 39

(2R, 3S) or (2S, 3S)-4-[1-(2-Hydroxy-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol

see Example 40.

Example 40

(2S, 3S) or (2R, 3S)-4-[1-(2-Hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol(S)-4-(pyrrolidin-3-yl-sulfanyl)-phenol hydrobromide (1 g, 3.6 mmol), (RS)-2-phenethyl-oxirane (0.8 g, 5.4 mmol) and triethylamine (0.76 ml, 5.4 mmol) were suspended in MeOH (20 ml). After 4 hours refluxing, the reaction mixture was cooled to room temperature and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 1:1 then 1:4) to provide (2R, 3S) or (2S, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol (0.1 g, first fraction, 8%) as a colorless oil (Example 39) MS: m/e = 344.4 ($M+H^+$) and (2S, 3S) or (2R, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol (0.13 g, second fraction, 10%) as a colorless oil (Example 40) MS: m/e = 344.3 ($M+H^+$).(RS)-2-Phenethyl-oxirane is a known compound and has been prepared as described in the following reference: S. Levy; Bull. Soc. Chim. Fr.; 49; 1931; 1823-1826.

Following the general method of examples 39 and 40, compounds of example 41 to example 46 were prepared.

Example 41

(2S, 3R) or (2R, 3R)-4-[1-(2-Hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol

The title compound, MS: m/e = 344.4 ($M+H^+$) was prepared from (R)-4-(pyrrolidin-3-yl-sulfanyl)-phenol trifluoro-acetic acid and (RS)-2-phenethyl-oxirane.

Example 42

(2R, 3R) or (2S, 3R)-4-[1-(2-Hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol

The title compound, MS: m/e = 344.4 ($M+H^+$) was prepared from (R)-4-(pyrrolidin-3-yl-sulfanyl)-phenol trifluoro-acetic acid and (RS)-2-phenethyl-oxirane.

Example 43

(2R, 3S) and (2S, 3S)-4-[1-(2-Hydroxy-2-indan-2-yl-ethyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 388.3 ($M+H^+$) was prepared from (S)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid and (RS)-2-indan-2-yl-oxirane.

Example 44

(2RS, 3RS) and (2RS, 3SR)-4-[1-(2-Hydroxy-4-phenyl-butyl)-piperidin-3-yl-sulfanyl]-phenol

The title compound, MS: m/e = 358.2 ($M+H^+$) was prepared from (RS)-4-(piperidin-3-yl-sulfanyl)-phenol hydrobromide and (RS)-2-phenethyl-oxirane.

Example 45

(3S, cis) or (3S, trans)-4-[1-(1-Hydroxy-3-phenyl-cyclobutylmethyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 388.3 ($M+H^+$) was prepared from (S)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid and cis or trans-5-phenyl-1-oxa-spiro[2.3]hexane.

Example 46

(3S, trans) or (3S, cis)-4-[1-(1-Hydroxy-3-phenyl-cyclobutylmethyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 388.2 ($M+H^+$) was prepared from (S)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid and trans or cis-5-phenyl-1-oxa-spiro[2.3]hexane.

Example 47

(RS)-4-[1-(4-Phenyl-but-2-ynyl)-pyrrolidine-3-sulfonyl]-phenol

(RS)-4-(Pyrrolidine-3-sulfonyl)-phenol trifluoro-acetic acid (0.2 g, 0.59 mmol) and $NaHCO_3$ (74 mg, 0.88 mmol) were suspended in MeOH (2 ml). After 10 minutes, reaction mixture was concentrated. The residue was taken up in $CHCl_3$. The resulting solid was filtrated and the filtrate was concentrated. The so-obtained foam was dissolved in dioxane (2 ml) and treated successively with paraformaldehyde (17.6 mg, 0.586 mmol), 3-phenyl-1-propyne (68 mg, 0.586 mmol) and CuCl (6.2 mg, 0.062 mmol). The reaction mixture was stirred at 100 °C for 0.75 hour then cooled to room temperature and concentrated. The residue was treated with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH 19:1) to provide (RS)-4-[1-(4-phenyl-but-2-ynyl)-pyrrolidine-3-sulfonyl]-phenol (0.14 g, 69%) as an orange foam, MS: m/e = 356.3 ($M+H^+$).

Example 48

(RS)-4-[1-(4-m-Tolyl-butyl)-pyrrolidine-3-sulfonyl]-phenol

To a 0 °C solution of (RS)-4-(1-but-3-enyl-pyrrolidine-3-sulfonyl)-phenol (0.106 g, 0.378 mmol) in THF (0.5 ml), 9-BBN (1.66 ml, 0.74 ml, 0.5 M solution in THF) was added dropwise. The reaction mixture was allowed to warm up slowly to room temperature. After 4 hours stirring, the reaction mixture was treated successively with DMF (1.5 ml), 3-bromotoluene (0.046 ml, 0.377 mmol), $PdCl_2(dppf)_2$-dichloromethane complex (9.3 mg, 0.01 mmol), and K_2CO_3 (95 mg, 0.69 mmol). After 5 hours stirring at 60 °C, the reaction mixture was cooled to room temperature, quenched with ethylacetate and H_2O. The aqueous phase was extracted with ethylacetate. The combined organic phases were washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed

over silica gel (CH_2Cl_2-MeOH, 98:2) to provide (RS)-4-[1-(4-m-tolyl-butyl)-pyrrolidine-3-sulfonyl]-phenol (66 mg, 47%) as a light yellow foam, MS: m/e = 374.4 ($M+H^+$).

Following the general method of example 48 the compounds of example 49 to example 50 were prepared.

Example 49

(RS)-4-{1-[4-(2-Methoxymethoxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol

The title compound, MS: m/e = 420.3 ($M+H^+$) was prepared from (RS)-4-(1-but-3-enyl-pyrrolidine-3-sulfonyl)-phenol and 1-iodo-2-methoxymethoxy-benzene.

1-Iodo-2-methoxymethoxy-benzene is a known compound and has been prepared as described in the following reference: J. R. Labrosse; C. Poncet; P. Lhoste; D. Sinou; Tetrahedron: Asymmetry; 10; 6; 1999; 1069-1078

Example 50

(RS)-4-{1-[4-(3-Benzyloxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol

The title compound, MS: m/e = 464.3 ($M-H^+$) was prepared from (RS)-4-(1-but-3-enyl-pyrrolidine-3-sulfonyl)-phenol and benzyl-(3-iodo-phenyl)-ether.

Benzyl-(3-iodo-phenyl)-ether is a known compound and has been prepared as described in the following reference: W. Kipping; J. Chem. Soc.; 1957; 3246-3250

Example 51

(RS)-4-{1-[4-(3-Hydroxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol

(RS)-4-{1-[4-(3-Benzyloxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol (88.4 mg, 0.2 mmol) and Pd/C (40 mg, 10% Pd on charcoal) in MeOH (5 ml) were refluxed for 2 hours under an atmospheric pressure of hydrogen. The reaction mixture was then cooled to room temperature, the catalyst was filtered and the filtrate was concentrated. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 19:1) to provide (RS)-4-{1-[4-(3-hydroxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol (53 mg, 69%) as a light beige solid, MS: m/e = 376.3 ($M+H^+$).

Following the general method of example 51 the compounds of example 52 to example 54 were prepared.

Example 52

(RS)-4-{1-[4-(4-Hydroxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol

The title compound, MS: m/e = 376.4 ($M+H^+$) was prepared from (RS)-4-{1-[4-(4-benzyloxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol.

Example 53

(RS)-(4-Pyridin-3-yl-butyl)-pyrrolidine-3-sulfonyl]-phenol

The title compound, MS: m/e = 361.2 ($M+H^+$) was prepared from (RS)-4-[1-(4-pyridin-3-yl-but-3-enyl)-pyrrolidine-3-sulfonyl]-phenol.

Example 54

(3RS, 4SR)-4-(4-Hydroxy-benzenesulfonyl)-1-(4-phenyl-butyl)-pyrrolidin-3-ol

The title compound, MS: m/e = 376.4 ($M+H^+$) was prepared from (3RS, 4SR)-4-(4-benzyloxy-benzenesulfonyl)-1-(4-phenyl-butyl)-pyrrolidin-3-ol.

Example 55

(RS)-4-{1-[4-(2-Hydroxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol

(RS)-4-{1-[4-(2-Methoxymethoxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol (34 mg, 0.08 mmol) in *i*PrOH (1 ml) was treated with HCl/Et_2O (1 ml). After 45 hours stirring at room temperature, the reaction mixture was quenched with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 19:1) to provide (RS)-4-{1-[4-(2-hydroxy-phenyl)-butyl]-pyrrolidine-3-sulfonyl}-phenol (17 mg, 56%) as a beige foam, MS: m/e = 376.4 ($M+H^+$).

Example 56

(3RS, 3RS) and (3RS, 3SR)-4-[1-(3-Hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol

(RS)-4-[3-(4-Hydroxy-phenylsulfanyl)-pyrrolidin-1-yl]-1-phenyl-butan-2-one (200 mg, 0.6 mmol) in MeOH (3 ml) was treated with $NaBH_4$ (33.2 mg, 0.9 mmol). After 15 minutes stirring at room temperature, the reaction mixture was acidified to pH 3 with 1N HCl then basified to pH 8 with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (ethylacetate) to provide (3RS, 3RS) and (3RS, 3SR)-4-[1-(3-hydroxy-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol (187 mg, 93%) as a white foam, MS: m/e = 344.3 ($M+H^+$).

Example 57

(RS)-4-[1-(1-Phenyl-piperidin-4-yl)-pyrrolidine-3-sulfonyl]-phenol

(RS)-4-(1-Piperidin-4-yl-pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid (53.8 mg, 0.1 mmol), Et_3N (50.5 mg, 0.5 mmol), phenylboronic acid (36.6 mg, 0.3 mmol) and copper(II) acetate (36 mg, 0.2 mmol) were suspensed in CH_2Cl_2 (2 ml). After 3.5 hours stirring at room temperature, the reaction mixture was directly chromatographed over

silica gel (CH_2Cl_2-MeOH 98:2 then 95:5) to provide (RS)-4-[1-(1-phenyl-piperidin-4-yl)-pyrrolidine-3-sulfonyl]-phenol (10 mg, 26%) as a white foam, MS: m/e = 387.3 ($M+H^+$).

Example 58

(2R,3R, S-oxide R)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol

(2RS,3R)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol (0.56 g, 1.62 mmol) was dissolved in MeOH (50 ml), cooled to 0 °C and treated with oxone (0.5 g, 0.81 mmol). After 4 hours stirring at 0 °C, reaction mixture was quenched with saturated $NaHCO_3$ (65 ml). Aqueous phase was extracted with CH_2Cl_2 (6 times). Combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. The residue was chromatographed by MPLC over silica gel (CH_2Cl_2-MeOH, 99:1 then 98:2) then by preparative HPLC (EtOH-heptane, 08:92, detection at 254 nm) to provide (2R,3R, S-oxide R)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol (30 mg, first fraction, 5%), MS: m/e = 362.2 ($M+H^+$).

Example 59

(2S,3R, S-oxide R)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol

The title compound was prepared in accordance with example 58 to provide (2S,3R, S-oxide R)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol (27 mg, second fraction, 4.7 %), MS: m/e = 362.2 ($M+H^+$).

Example 60

(2RS,3R, S-oxide S)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol hydrochloride

The title compound was prepared in accordance with example 58 to provide (2RS,3R, S-oxide S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol hydrochloride (100 mg, third fraction, 17 %), MS: m/e = 362.2 ($M+H^+$).

Following the general method of examples 58 – 60, the compounds of example 61 to 63 were prepared.

Example 61

(2RS,3S, S-oxide S)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol hydrochloride

The title compound, MS: m/e = 362.2 ($M+H^+$) was prepared from (2RS,3S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol.

Example 62

(2S,3S, S-oxide R)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol

The title compound, MS: m/e = 362.2 ($M+H^+$) was prepared from (2RS,3S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol.

Example 63

(2R,3S, S-oxide R)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol

The title compound, MS: m/e = 362.2 ($M+H^+$) was prepared from (2RS,3S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol.

Example 64

(3S, S-oxide R) or (3S, S-oxide S)-4-[1-(2,2-Difluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol

(3S)-4-[1-(2,2-Difluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol (0.25 g, 0.688 mmol) was dissolved in MeOH (20 ml), cooled to 0 °C and treated with oxone (0.21 g, 0.34 mmol). After 4 hours stirring at 0 °C, reaction mixture was quenched with saturated $NaHCO_3$ (65 ml). Aqueous phase was extracted with CH_2Cl_2 (3 times). Combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. The residue was chromatographed by MPLC over silica gel (hexane-ethyl acetate, 98:2 to 50:50) to provide (3S, S-oxide R) or (3S, S-oxide S)-4-[1-(2,2-difluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol (140 mg, first fraction, 54%), MS: m/e = 380.4 ($M+H^+$).

Example 65

(3S, S-oxide S) or (3S, S-oxide R)-4-[1-(2,2-Difluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol

The title compound was prepared in accordance with example 64 to provide (3S, S-oxide S) or (3S, S-oxide R)-4-[1-(2,2-difluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol (72 mg, second fraction, 28 %), MS: m/e = 380.4 ($M+H^+$).

Following the general method of example 64 and 65, the compounds of example 66 and 67 were prepared.

Example 66

(3R, S-oxide R) or (3R, S-oxide S)-4-[1-(2,2-Difluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol

The title compound, MS: m/e = 380.3 ($M+H^+$) was prepared from (3R)-4-[1-(2,2-difluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol.

Example 67

(3R, S-oxide S) or (3R, S-oxide R)-4-[1-(2,2-Difluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol

The title compound, MS: m/e = 380.3 ($M+H^+$) was prepared from (3R)-4-[1-(2,2-difluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol.

Example 68

(2RS,3S)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol

(2RS,3S)-2-Fluoro-1-[3-(4-hydroxy-phenylsulfanyl)-pyrrolidin-1-yl]-4-phenyl-butan-1-one (200 mg, 0.56 mmol) was dissolved in THF (4 ml). Borane-dimethylsulfide complex (170 µl, 1.67 mmol) was added.The mixture was refluxed for 7 hours and then cooled to 0 °C. MeOH (0.7 ml) was added dropwise and the solvent was removed in vacuo.The residue was dissolved with THF (3.5 ml) and 5N HCl (1.1 ml) and was stirred at 60 °C for 12 hours.The solvent was removed in vacuo and the residue was taken up in saturated $NaHCO_3$ (3 ml).The aqueous layer was extracted with CH_2Cl_2 (3 times).The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 99:1) to provide (2RS,3S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol (134 mg, 70%) as colorless oil, MS: m/e = 346.3 ($M+H^+$).

Following the general method of example 68 the compound of example 69 was prepared.

Example 69

(2RS,3R)-4-[1-(2-Fluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol

The title compound, MS: m/e = 346.3 ($M+H^+$) was prepared from (2RS,3R)-2-fluoro-1-[3-(4-hydroxy-phenylsulfanyl)-pyrrolidin-1-yl]-4-phenyl-butan-1-one.

Synthesis of intermediates.

Example 70

(RS)-4-[3-(4-Hydroxy-phenylsulfanyl)-pyrrolidin-1-yl]-1-phenyl-butan-2-one

(RS)-4-(Pyrrolidin-3-ylsulfanyl)-phenol hydrobromide (470 mg, 1.7 mmol), Et_3N (0.35 ml, 2.5 mmol) and 1-phenyl-3-buten-2-one (0.25 g, 1.7 mmol) were suspended in CH_2Cl_2 (10 ml). After stirring overnight at room temperature, the reaction mixture was concentrated and chromatographed over silica gel (hexane-ethylacetate 1:1 then ethylacetate) to provide (RS)-4-[3-(4-hydroxy-phenylsulfanyl)-pyrrolidin-1-yl]-1-phenyl-butan-2-one (90 mg, 16%) as a brown oil, MS: m/e = 342.2 ($M+H^+$).

1-Phenyl-3-buten-2-one is a known compound and has been prepared as described in the

following reference: E. Negishi; V. Bagheri; S. Chatterjee; M. Fen-Tair; J. A. Miller; T. A. Stoll; Tetrahedron Lett.; 24; 47; 1983; 5181-5184.

Example 71

(RS)-4-(1-But-3-enyl-pyrrolidine-3-sulfonyl)-phenol

The title compound, MS: m/e = 282.1 ($M+H^+$), has been prepared according to the procedure described for example 31 from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid salt and 4-bromo-butene.

Example 72

(3RS, 4SR)-4-(4-Benzyloxy-benzenesulfonyl)-1-(4-phenyl-butyl)-pyrrolidin-3-ol

The title compound, MS: m/e = 466.3 ($M+H^+$), has been prepared according to the procedure described for example 1, from (3RS, 4SR)-4-(4-benzyloxy-benzenesulfonyl)-pyrrolidin-3-ol trifluoro-acetic acid and 4-phenyl-butyraldehyde.

Example 73

(RS)-4-[1-(4-Pyridin-3-yl-but-3-enyl)-pyrrolidine-3-sulfonyl]-phenol

(RS)-4-(1-But-3-enyl-pyrrolidine-3-sulfonyl)-phenol (100 mg, 0.355 mmol), 3-bromopyridine (62 mg, 0.39 mmol), $PdCl_2(dppf)_2$-dichloromethane complex (9.3 mg, 0.01 mmol), and K_2CO_3 (95 mg, 0.69 mmol) were suspended in DMF (1.5 ml). After 5 hours stirring at 80 °C, the reaction mixture was cooled to room temperature and concentrated. The residue was chromatographed over silica gel (CH_2Cl_2/MeOH 97:3 then 19/1) to provide (RS)-4-[1-(4-pyridin-3-yl-but-3-enyl)-pyrrolidine-3-sulfonyl]-phenol (100 mg, 78%) as a light orange foam, MS: m/e = 359.2 ($M+H^+$).

Example 74

(RS)-4-(Pyrrolidin-3-ylsulfanyl)-phenol hydrobromide

(RS)-4-[1-(Toluene-4-sulfonyl)-pyrrolidin-3-ylsulfanyl]-phenol (1.9 g, 5.44 mmol) in phenol (5.1 g, 54.4 mmol) was treated with HBr (25 ml, 48%). After 4 hours stirring at 100 °C, the reaction mixture was cooled to room temperature and quenched with H_2O and CH_2Cl_2. The aqueous phase was washed with CH_2Cl_2 and concentrated to provide (RS)-4-(pyrrolidin-3-ylsulfanyl)-phenol hydrobromide (1.13 g, 75%) as a brown oil, MS: m/e = 196.2 ($M+H^+$).

Following the general method of example 74, the compounds of example 75 to example 77

were prepared.

Example 75

(S)-4-(Pyrrolidin-3-ylsulfanyl)-phenol hydrobromide

The title compound, MS: m/e = 196.2 ($M+H^+$) and $[\alpha]_D^{20}$ = -20.41 ° (c = 1.02, MeOH) was prepared from (S)-4-[1-(toluene-4-sulfonyl)-pyrrolidin-3-ylsulfanyl]-phenol.

Example 76

(RS)-4-(Piperidin-3-ylsulfanyl)-phenol hydrobromide

The title compound, MS: m/e = 210.3 ($M+H^+$) was prepared from (RS)-4-[1-(toluene-4-sulfonyl)-piperidin-3-ylsulfanyl]-phenol.

Example 77

(RS)-3-(Pyrrolidin-3-ylsulfanyl)-phenol hydrochloride

The title compound, MS: m/e = 196.2 ($M+H^+$) was prepared from (RS)-3-(3-methoxy-phenylsulfanyl)-1-(toluene-4-sulfonyl)-pyrrolidine.

Example 78

(R)-4-(Pyrrolidin-3-ylsulfanyl)-phenol trifluoroacetic acid

(R)-3-(4-Hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (3.0 g, 10.2 mmol) in CH_2Cl_2 (36 ml) was treated with trifluoroacetic acid (7.8 ml, 0.1 mol). After 1 hour stirring at room temperature, the reaction mixture was concentrated to provide (R)-4-(pyrrolidin-3-yl-sulfanyl)-phenol trifluoroacetic acid (3.46 g) as an orange oil, MS: m/e = 196.2 ($M+H^+$) and $[\alpha]_D^{20}$ = +25.06 ° (c = 1.2, MeOH).

Following the general method of example 78 the compounds of example 79 to example 86 were prepared.

Example 79

(RS)-4-(Pyrrolidine-3-sulfonyl)-phenol trifluoro acetic acid

The title compound, MS: m/e = 228.1 ($M+H^+$) was prepared from (RS)-3-(4-hydroxy-benzenesulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 80

(S)-4-(Pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid

The title compound, MS: m/e = 228.1 ($M+H^+$) and $[\alpha]_D^{20}$ = -3.45 ° (c = 0.99, MeOH) was prepared from (S)-3-(4-hydroxy-benzenesulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 81

(3RS, 4RS)-4-(4-Hydroxy-benzenesulfonyl)-pyrrolidin-3-ol

The title compound, MS: m/e = 244.2 ($M+H^+$) was prepared from 3-hydroxy-4-(4-hydroxy-benzenesulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 82

(3RS, 4SR)-4-(4-Benzyloxy-benzenesulfonyl)-pyrrolidin-3-ol trifluoroacetic acid

The title compound, MS: m/e = 334.2 ($M+H^+$) was prepared from (3RS, 4SR)-3-(4-benzyloxy-benzenesulfonyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 83

(RS)-5-(Pyrrolidine-3-sulfonyl)-1H-indazole trifluoroacetic acid

The title compound, MS: m/e = 252.2 ($M+H^+$) was prepared from (RS)-5-(1-tert-butoxycarbonyl-pyrrolidine-3-sulfonyl)-indazole-1-carboxylic acid tert-butyl ester.

Example 84

(RS)-5-(Pyrrolidine-3-sulfonyl)-1,3-dihydro-indol-2-one trifluoroacetic acid

The title compound, MS: m/e = 267.0 ($M+H^+$) was prepared from (RS)-3-(2-oxo-2,3-dihydro-1H-indole-5-sulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 85

(RS)-6-(Pyrrolidine-3-sulfonyl)-3H-benzooxazol-2-one trifluoroacetic acid

The title compound, MS: m/e = 269.2 ($M+H^+$) was prepared from (RS)-3-(2-oxo-3-trityl-2,3-dihydro-benzooxazole-6-sulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 86

(RS)-4-(1-Piperidin-4-yl-pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid

The title compound, MS: m/e = 311.3 ($M+H^+$) was prepared from (RS)-4-[3-(4-hydroxy-benzenesulfonyl)-pyrrolidin-1-yl]-piperidine-1-carboxylic acid tert-butyl ester.

Example 87

4-(Azetidine-3-sulfonyl)-phenol

The title compound, MS: m/e = 214.2 ($M+H^+$) was prepared from 4-(1-benzhydryl-azetidine-3-sulfonyl)-phenol following the procedure described for example 51

Example 88

(RS)-3-(4-Hydroxy-benzenesulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

(RS)-3-(4-Hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.95 g, 6.6 mmol) was dissolved in MeOH (30 ml) and treated with oxone® (6.10 g, 9.9 mmol). After 3.5 hours stirring at room temperature, the reaction mixture was filtered and the filtrate was neutralized with saturated $NaHCO_3$. The aqueous phase was extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (hexane-ethyl acetate 4:1 then 1:1) to provide (RS)-3-(4-hydroxy-benzenesulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (1.27 g, 58.8%) as a white foam, MS: m/e = 328.2 ($M+H^+$).

Following the general method of example 88 the compounds of example 89 to example 91 were prepared

Example 89

(S)-3-(4-Hydroxy-benzenesulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 326.3 ($M-H^+$) and $[\alpha]_D^{20}$ = -25.72 ° (c = 1.07, chloroform) was prepared from (S)-3-(4-hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Example 90

(3RS, 4RS)-3-Hydroxy-4-(4-hydroxy-benzenesulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 344.4 ($M-H^+$) was prepared from (3RS, 4RS)-3-hydroxy-4-(4-hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 91

4-(1-Benzhydryl-azetidine-3-sulfonyl)-phenol

The title compound, MS: m/e = 380.3 ($M+H^+$) was prepared from 4-(1-benzhydryl-azetidin-3-ylsulfanyl)-phenol.

Example 92

(RS)-5-(1-tert-Butoxycarbonyl-pyrrolidine-3-sulfonyl)-indazole-1-carboxylic acid tert-butyl ester

(RS)-5-(1-tert-Butoxycarbonyl-pyrrolidin-3-ylsulfanyl)-indazole-1-carboxylic acid tert-butyl ester (0.175 g, 0.41 mmol) was dissolved in CH_2Cl_2 (10 ml), cooled to 0 °C and treated with m-CPBA (0.26 g, 1.04 mmol, 70% of peracid). After 1 hour stirring at 0 °C, the reaction mixture was quenched with saturated $NaHCO_3$. The organic phase was washed with saturated $NaHCO_3$, dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (hexane-ethyl acetate 9:1 then 4:1 then 2:1) to provide (RS)-5-(1-tert-butoxycarbonyl-pyrrolidine-3-sulfonyl)-indazole-1-carboxylic acid tert-butyl ester (0.127 g, 67.4%) as a white foam, MS: m/e = 452.3 ($M+H^+$).

Following the general method of example 92 the compounds of example 93 to example 94 were prepared.

Example 93

(RS)-3-(2-Oxo-3-trityl-2,3-dihydro-benzooxazole-6-sulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 628.1 ($M+NH_4^+$) was prepared from (RS)-3-(2-oxo-3-trityl-2,3-dihydro-benzooxazol-6-yl-sulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl.

Example 94

(RS)-3-(2-Oxo-2,3-dihydro-1H-indole-5-sulfonyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 384.2 ($M+NH_4^+$) was prepared from (RS)-3-(2-oxo-2,3-dihydro-1H-indol-5-yl-sulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 95

(3RS, 4SR)-3-(4-Benzyloxy-benzenesulfonyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

(RS)-3-(4-Benzyloxy-benzenesulfonyl)-4-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (13.4 mg, 0.031 mmol) was dissolved in MeOH (0.5 ml), cooled to 0 °C and treated with $NaBH_4$ (1.64 mg, 0.043 mmol). After 0.5 hour stirring at 0 °C, the reaction mixture was acidified to pH 1 with 1N HCl. The aqueous phase was extracted with CH_2Cl_2. The combined organic phases were washed with H_2O, dried over Na_2SO_4, filtered and the

solvent was evaporated to provide (3RS, 4SR)-3-(4-benzyloxy-benzenesulfonyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (12.3 mg, 92%) as a white solid, MS: m/e = 434.4 ($M+H^+$).

Example 96

(RS)-3-(4-Benzyloxy-benzenesulfonyl)-4-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester

(3RS, 4RS)-3-(4-Benzyloxy-benzenesulfonyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (50 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (2 ml) and treated successively with 4Å molecular sieves (56 mg, powder) and pyridinium dichromate (56.4 mg, 0.15 mmol). After 3 hours stirring at room temperature, the reaction mixture was directly chromatographed over silica gel (hexane-ethyl acetate 4:1 then 1:1) to provide (RS)-3-(4-benzyloxy-benzenesulfonyl)-4-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester (27 mg, 48%) as an oil, MS: m/e = 374.2 (M-*t*butyl).

Example 97

(3RS, 4RS)-3-(4-Benzyloxy-benzenesulfonyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 434.3 ($M+H^+$) was prepared from (3RS, 4RS)-3-(4-benzyloxy-phenylsulfanyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester following the procedure described for example 88.

Example 98

(3RS, 4RS)-3-(4-Benzyloxy-phenylsulfanyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester

(3RS, 4RS)-3-Hydroxy-4-(4-hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.2 g, 0.6 mmol) was dissolved in acetone (5 ml), and treated with K_2CO_3 (0.1 g, 0.7 mmol). After 1 hour refluxing, the reaction mixture was cooled to room temperature and benzylbromide (0.084 ml, 0.7 mmol) was added. Reaction mixture was refluxed for an additional 3 hours then cooled to room temperature and quenched with H_2O. The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (hexane-ethyl acetate 2:1) to provide (3RS, 4RS)-3-(4-benzyloxy-phenylsulfanyl)-4-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (0.208 g, 81%) as a yellow oil, MS: m/e = 402.4 ($M+H^+$).

Example 99

(RS)-4-[3-(4-Hydroxy-benzenesulfonyl)-pyrrolidin-1-yl]-piperidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 411.3 ($M+H^+$) was prepared from (RS)-4-(pyrrolidine-3-sulfonyl)-phenol trifluoroacetic acid and 4-oxo-piperidine-1-carboxylic acid tert-butyl ester following the procedure described for example 1.

Example 100

(RS)-3-(4-Hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

(RS)-3-(Toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.8 g, 2.34 mmol), 4-mercaptophenol (0.49 g, 3.88 mmol, 90%) and Na_2CO_3 (0.37 g, 3.51 mmol) were suspended in acetonitrile (10 ml). After 20 hours refluxing, reaction mixture was concentrated. The residue was taken up in H_2O (15 ml) and extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated. The residue was chromatographed over silica gel (hexane-ethylacetate 4:1 then 2:1) to provide (RS)-3-(4-hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.56 g, 81%) as a slightly yellow solid, MS: m/e = 296.4 ($M+H^+$).(RS)-3-(Toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester is a known compound and has been prepared as described in WO 9734895

Following the general method of example 100, the compounds of example 101 to example 108 were prepared.

Example 101

(R)-3-(4-Hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 295.1 (M^+) and $[\alpha]_D^{20}$ = +20.09 ° (c = 0.61, chloroform) was prepared from (S)-3-(toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester.

Example 102

(S)-3-(4-Hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 294.3 ($M-H^+$) and $[\alpha]_D^{20}$ = -18.43 ° (c = 0.52, chloroform) was prepared from (R)-3-(toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester.

(R)-3-(Toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester is a known compound and has been prepared as described in the following reference: U. Nagel; H. G. Nedden; Chem. Ber., Recl.; 130; 3; 1997; 385-398.

Example 103

(3RS, 4RS)-3-Hydroxy-4-(4-hydroxy-phenylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 312.2 ($M+H^+$) was prepared from 6-oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester.

6-Oxa-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester is a known compound and has been prepared as described in the following reference: C. Y. Hong; Y. K. Kim; Y. H. Lee; J. H. Kwak; Bioorg. Med. Chem. Lett.; 8; 3; 1998; 221-226

Example 104

4-(1-Benzhydryl-azetidin-3-ylsulfanyl)-phenol

The title compound, MS: m/e = 348.4 ($M+H^+$) was prepared from methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester by using DMF as solvent instead of acetonitrile.

Methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester is a known compound and has been prepared as described in the following reference: N. I. Carruthers; S. Wong; T. Chan; J. Chem. Res. Synop.; 9; 1996; 430-431.

Example 105

(S)-4-[1-(Toluene-4-sulfonyl)-pyrrolidin-3-ylsulfanyl]-phenol

The title compound, MS: m/e = 349.1 (M^+) and $[\alpha]_D^{20}$ = -41.41 ° (c = 1.10, chloroform) was prepared from (R)-toluene-4-sulfonic acid 1-(toluene-4-sulfonyl)-pyrrolidin-3-yl ester by using DMF as solvent instead of acetonitrile.

(R)-Toluene-4-sulfonic acid 1-(toluene-4-sulfonyl)-pyrrolidin-3-yl ester is a known compound and has been prepared as described in the following reference: A. Corruble; J. Y. Valnot; J. Maddaluno; P. Duhamel; J. Org. Chem.; Vol. 63; 23; 8274

Example 106

(RS)-4-[1-(Toluene-4-sulfonyl)-pyrrolidin-3-ylsulfanyl]-phenol

The title compound, MS: m/e = 349.1 (M^+) was prepared from (RS)-toluene-4-sulfonic acid 1-(toluene-4-sulfonyl)-pyrrolidin-3-yl ester by using DMF as solvent instead of acetonitrile.

(RS)-Toluene-4-sulfonic acid 1-(toluene-4-sulfonyl)-pyrrolidin-3-yl ester is a known compound and has been prepared as described in the following reference: J. R. Shanklin; C. P. Johnson; A. G. Proakis; R. J. Barrett; J. Med. Chem.; 1991; 34; 10; 3011-3022

Example 107

(RS)-4-[1-(Toluene-4-sulfonyl)-piperidin-3-ylsulfanyl]-phenol

The title compound, MS: m/e = 363.0 (M^+) was prepared from (RS)-toluene-4-sulfonic acid 1-(toluene-4-sulfonyl)-piperidin-3-yl ester by using DMF as solvent instead of acetonitrile.

(RS)-Toluene-4-sulfonic acid 1-(toluene-4-sulfonyl)-piperidin-3-yl ester is a known compound and has been prepared as described in the following reference: J. R. Shanklin; C. P. Johnson; A. G. Proakis; R. J. Barrett; J. Med. Chem.; 1991; 34; 10; 3011-3022

Example 108

(RS)-3-(3-Methoxy-phenylsulfanyl)-1-(toluene-4-sulfonyl)-pyrrolidine

The title compound, MS: m/e = 363.1 (M^+) was prepared from (RS)-toluene-4-sulfonic acid 1-(toluene-4-sulfonyl)-pyrrolidin-3-yl ester and 3-methoxythiophenol and by using DMF as solvent instead of acetonitrile.

Example 109

(S)-3-(Toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

To a 0 °C solution of (S)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (8.5 g, 45.4 mmol), triethylamine (9.47 ml, 68.1 mmol) and dimethylaminopyridine (0.55 g, 4.5 mmol) in CH_2Cl_2 (150 ml) was added portionwise *p*-toluenesulfonyl chloride (9.52 g, 49.9 mmol). After 48 hours stirring at room temperature, reaction mixture was acidified to pH 1 with 1N HCl and aqueous phase was extracted with CH_2Cl_2. Combined organic phases were washed with 1N HCl and H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 9:1 then 8:2 then 1:1) to provide (S)-3-(toluene-4-sulfonyloxy)-pyrrolidine-1-carboxylic acid tert-butyl ester (13.1 g, 87%) as a slightly yellow oil, MS: m/e = 268.1 (M-O*t*Bu) and $[\alpha]_D^{20} = +17.55$ ° (c = 3.33, diethylether).

(S)-3-Hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester is a known compound and has been prepared as described in the following reference: U. Nagel; H. G. Nedden; Chem. Ber.; Recl.; 130; 3; 1997; 385-398

Following the general method of example 109, the compounds of example 110 to example 111 were prepared.

Example 110

(RS)-Toluene-4-sulfonic acid 2-fluoro-4-phenyl-butyl ester

The title compound, MS: m/e = 322.1 (M^+) was prepared from (RS)-2-fluoro-4-phenyl-butan-1-ol.

Example 111

Toluene-4-sulfonic acid 2-(2-hydroxy-indan-2-yl)-ethyl ester

The title compound, MS: m/e = 355.2 ($M+Na^+$) was prepared from 2-(2-hydroxy-ethyl)-indan-2-ol.

Example 112

(RS)-2-(2-Bromo-ethyl)-1,2,3,4-tetrahydro-naphthalen-2-ol

To a 0 °C solution of triphenylphosphine (1.03 g, 3.93 mmol), in CH_2Cl_2 (15 ml) was added slowly a solution of bromine (0.192 ml, 3.74 mmol) in CH_2Cl_2. After 1 hour stirring at room temperature, the reaction mixture was cooled to 0 °C and treated slowly with a solution of (RS)-2-(2-hydroxy-ethyl)-1,2,3,4-tetrahydro-naphthalen-2-ol (0.72 g, 3.74 mmol) in CH_2Cl_2 (15 ml). After 1.5 hour stirring at room temperature, the reaction mixture was again cooled to 0 °C, treated slowly with triethylamine (0.52 ml, 3.74 mmol), washed successively with H_2O and brine, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 9:1) to provide (RS)-2-(2-bromo-ethyl)-1,2,3,4-tetrahydro-naphthalen-2-ol (0.58 g, 61%) as a colorless oil, MS: m/e = 255.1 (M^+).

Example 113

(RS)-2-Fluoro-4-phenyl-butan-1-ol

To a 0 °C suspension of $LiAlH_4$ (0.4 g, 10.6 mmol) in dry THF (5 ml) was added dropwise a solution of (RS)-2-fluoro-4-phenyl-butyric acid methyl ester (1 g, 5.3 mmol) in dry THF (10 ml). After 1 hour stirring at 0 °C, the reaction mixture was quenched successively with H_2O (0.4 ml), 5N NaOH (0.4 ml) and again H_2O (1.2 ml). The resulting solid was filtered and the filtrate was concentrated to provide (RS)-2-fluoro-4-phenyl-butan-1-ol (0.89 g, 99%) as a colorless oil, MS: m/e = 168.1 (M^+).

Following the general method of example 113, the compounds of example 114 to example 115 were prepared.

Example 114

2-(2-Hydroxy-ethyl)-indan-2-ol

The title compound, MS: m/e = 178.1 (M^+) was prepared from (2-hydroxy-indan-2-yl)-acetic acid methyl ester.

(2-Hydroxy-indan-2-yl)-acetic acid methyl ester is a known compound and has been prepared as described in the following reference: H. R. Veen; H. Cerfontain; Can. J. Chem.; 62; 1984; 2202-2205.

Example 115

(RS)-2-(2-Hydroxy-ethyl)-1,2,3,4-tetrahydro-naphthalen-2-ol

The title compound, MS: m/e = 192.3 (M^+) was prepared from (RS)-(2-hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid methyl ester.

(RS)-(2-Hydroxy-1,2,3,4-tetrahydro-naphthalen-2-yl)-acetic acid methyl ester is a known compound and has been prepared as described in the following reference: H. R. Veen; H. Cerfontain; Can. J. Chem.; 62; 1984; 2202-2205.

Example 116

(RS)-5-(1-tert-Butoxycarbonyl-pyrrolidin-3-yl-sulfanyl)-indazole-1-carboxylic acid tert-butyl ester

To a room temperature solution of (RS)-3-(1H-indazol-5-ylsulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.2 g, 0.61 mmol), and dimethylaminopyridine (7.4 mg, 0.06 mmol) in CH_2Cl_2 (3 ml) was added slowly a solution of di-tert-butyl dicarbonate (0.13 g, 0.61 mmol) in CH_2Cl_2. After 30 minutes stirring at room temperature, the reaction mixture was washed with H_2O, dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 9:1 then 8:2) to provide (RS)-5-(1-tert-butoxycarbonyl-pyrrolidin-3-ylsulfanyl)-indazole-1-carboxylic acid tert-butyl ester (0.19 g, 74%) as a yellow oil, MS: m/e = 420.4 ($M+H^+$).

Example 117

(RS)-3-(2-Oxo-3-trityl-2,3-dihydro-benzooxazol-6-yl-sulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

Tris(dibenzylideneacetone)dipalladium chloroform complex (14 mg, 13.5 µmol) and 1,1'-bis(diphenylphosphino)ferrocene (30 mg, 54.1 µmol) in degassed and dry toluene (2 ml) were stirred at room temperature until the solution turned orange (15 minutes). 6-Bromo-3-trityl-3H-benzooxazol-2-one (0.2 g, 0.44 mmol), Cs_2CO_3 (0.22 g, 0.68 mmol) and (RS)-3-mercapto-pyrrolidine-1-carboxylic acid tert-butyl ester (0.1 g, 0.49 mmol) in toluene (0.5 ml) were successively added. After 4 hours stirring at 100 °C, the reaction mixture was cooled to room temperature and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 9:1 then 1:1) to provide (RS)-3-(2-oxo-3-trityl-2,3-dihydro-benzooxazol-6-yl-sulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester (0.19 g, 77%) as a white foam, MS: m/e = 596.1 ($M+NH_4^+$).

Following the general method of example 117 the compounds of example 118 to example 119 were prepared.

Example 118

(RS)-3-(1H-Indazol-5-yl-sulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 319.1 (M^+) was prepared from 5-iodo-1H-indazole.

5-Iodo-1H-indazole is a known compound and has been prepared as described in the following reference: L.Auwers; Chem. Ber.; 55; 1922; 1172.

Example 119

(RS)-3-(2-Oxo-2,3-dihydro-1H-indol-5-yl-sulfanyl)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound, MS: m/e = 334.4 (M^+) was prepared from 5-iodo-1,3-dihydro-indol-2-one.

Example 120

5-Iodo-1,3-dihydro-indol-2-one

A solution of 2-indolinone (2.66 g, 20 mmol) in acetic acid (20 ml) was stirred at room temperature in the presence of N-iodosuccinimide (5.4 g, 24 mmol) for 2 hours. H_2O (150 ml) was then added. The precipitate was filtered, washed with H_2O, and dried. The resulting solid was refluxed in ethyl acetate (50 ml), cooled to 0 °C, filtered, washed with ethylacetate and ether and dried to provide 5-iodo-1,3-dihydro-indol-2-one (3.62 g, 70%) as a beige solid, m.p. 190-192°C and MS: m/e = 259 (M^+).

Example 121

6-Bromo-3-trityl-3H-benzooxazol-2-one

6-Bromo-3H-benzooxazol-2-one (0.165 g, 0.77 mmol) was added portionwise into a 0 °C suspension of NaH (44.8 mg, 1 mmol, 55%) in dry DMF (4 ml). After 1 hour stirring at room temperature, a solution of triphenylmethylchloride (0.24 g, 0.85 mmol) in DMF (0.5 ml) was added. The reaction mixture was stirred 1 hour at room temperature then quenched with H_2O (15 ml). The aqueous phase was extracted with ethyl acetate, the combined organic phases were washed with H_2O and brine, dried over Na_2SO_4 and concentrated to provide 6-bromo-3-trityl-3H-benzooxazol-2-one (0.27 g, 77 %) as a beige solid, MS: m/e = 457.1 ($M+H^+$).

6-Bromo-3H-benzooxazol-2-one is a known compound and has been prepared as described in the following reference: H. Gershon; D. D. Clarke; M. Gershon; Monatsh. Chem.; 1993; 124; 4; 367-379

Example 122

(RS)-2-Fluoro-4-phenyl-butyric acid methyl ester

nBuLi (13.8 ml, 22 mmol, 1.6 M in hexan) was added dropwise into a 0 °C solution of diisopropylamine (3.39 ml, 24 mmol) in THF (34 ml). The reaction mixture was stirred at 0 °C for 15 minutes then cooled to –75 °C and treated slowly with a solution of methyl 4-phenylbutyrate (3.56 g, 20 mmol) in THF (10 ml). After 30 minutes stirring at –75 °C, trimethylchlorosilane (5.06 ml, 40 mmol) was added dropwise and the reaction mixture was allowed to warm up to room temperature. After 30 minutes, reaction mixture was concentrated, the residue was taken up in CH_2Cl_2 (100 ml), the resulting precipitate was filtrated, filtrate was cooled to 13 °C and subsequently treated slowly with a solution of N-fluorodibenzenesulfonimide (6.3 g, 20 mmol) in CH_2Cl_2 (50 ml). After 3 hours stirring at room temperature, the reaction mixture was washed with H_2O (2 times). The aqueous phase was extracted with CH_2Cl_2, the combined organic phases were dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 99:1 then 98:2) to provide (RS)-2-fluoro-4-phenyl-butyric acid methyl ester (2.47 g, 63 %) as a colorless oil, MS: m/e = 196.1 (M^+).

Methyl 4-phenylbutyrate is a known compound and has been prepared as described in the following reference: M. V. Bhatt; M. Ravindranathan; V. Somayaji; G. V. Rao; J. Org. Chem; 49; 17; 1984; 3170-3173.

Example 123

(RS)-3-Mercapto-pyrrolidine-1-carboxylic acid tert-butyl ester

To a 0 °C solution of (RS)-3-acetylsulfanyl-pyrrolidine-1-carboxylic acid tert-butyl ester (1.4 g, 5.07 mmol) in MeOH (15 ml) was added dropwise a suspension of sodium methoxide (0.61 g, 11.3 mmol) in MeOH. After 6 hours stirring at room temperature, the reaction mixture was neutralized with 1N HCl and MeOH was partially evaporated. H_2O and ethylacetate were added. The aqueous phase was extracted with ethylacetate, the combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to provide (RS)-3-mercapto-pyrrolidine-1-carboxylic acid tert-butyl ester (1.2 g, 100 %) as a colorless oil, MS: m/e = 130.1 (M-OtBu).

Example 124

(RS)-3-Acetylsulfanyl-pyrrolidine-1-carboxylic acid tert-butyl ester

To a 0 °C solution of triphenylphosphine (2.1 g, 8 mmol) in THF (14 ml) was added dropwise (15 minutes) diisopropylazodicarboxylate (1.55 ml, 8 mmol). After 30 minutes stirring at 0 °C, a solution containing (RS)-3-hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (1 g, 5.34 mmol) and thioacetic acid (0.57 ml, 8 mmol) in THF (7 ml) was added dropwise. The reaction mixture was stirred 30 minutes at 0 °C, 45 minutes at room temperature and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 9:1 then 8:2 then 1:1) to provide (RS)-3-acetylsulfanyl-pyrrolidine-1-

carboxylic acid tert-butyl ester (1.4 g, 100 %) as a slightly yellow oil, MS: m/e = 246.3 ($M+H^+$).

(RS)-3-Hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester is a known compound and has been prepared as described in the following reference: M. Bouygues; M. Medou; G. Quelever; J. C. Chermann; M. Camplo; J. L. Kraus; Bioorg. Med. Chem. Lett.; 8; 3; 1998; 277-280

Example 125

(RS)-2-Indan-2-yl-oxirane

To a mixture containing NaH (9.8 mg, 0.2 mmol) and trimethylsulfoxoniumiodide (57.8 mg, 0.26 mmol) was added slowly DMSO (0.44 ml). After 30 minutes stirring at room temperature, a solution of indan-2-carbaldehyde (32 mg, 0.22 mmol) in DMSO (0.1 ml) was added. The reaction mixture was stirred 18 hours at room temperature and then quenched with H_2O. The aqueous phase was extracted with ethylacetate, combined organic phases were dried over Na_2SO_4, filtered and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 98:2) to provide (RS)-2-indan-2-yl-oxirane (9 mg, 26 %) as a colorless oil, MS: m/e = 160.0 (M^+).

Indan-2-carbaldehyde is a known compound and has been prepared as described in the following reference: Kenner; J. Chem. Soc.; 105; 1914; 2694.

Example 126

trans or cis-5-Phenyl-1-oxa-spiro[2.3]hexane

see Example 127.

Example 127

cis or trans-5-Phenyl-1-oxa-spiro[2.3]hexane

To a solution of (3-methylene-cyclobutyl)-benzene (0.236 g, 1.64 mmol) in CH_2Cl_2 (3 ml) was added successively methyltrioxorhenium (4 mg, 0.016 mmol), pyridine (15 µl, 0.2 mmol) and H_2O_2 (0.22 ml, 35 %in H_2O). The reaction mixture was stirred 7 hours at room temperature, diluted with CH_2Cl_2, washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 98:2) to provide the compound of example 126 trans or cis-5-phenyl-1-oxa-spiro[2.3]hexane (90 mg, first fraction, 35 %) as a colorless oil, MS: m/e = 159.2 ($M-H^+$)

and

the compound of example 127 cis or trans-5-phenyl-1-oxa-spiro[2.3]hexane (56 mg, second fraction, 21 %) as a colorless oil, MS: m/e = 159.1 ($M-H^+$).

Example 128

(3-Methylene-cyclobutyl)-benzene

To a 2-3 °C suspension of methyltriphenylphosphonium bromide (0.36 g, 1 mmol) in THF (2.5 ml) was added dropwise n-BuLi (0.69 ml, 1.1 mmol, 1.6 M in hexan). After 1 hour stirring at 0 °C, a solution of 3-phenyl-cyclobutanone (0.146 g, 1 mmol) in THF (1.5 ml) was added dropwise. The reaction mixture was stirred 24 hours at room temperature and then diluted with hexane. The so obtained precipitate was filtered and the filtrate was concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 9:1) to provide (3-methylene-cyclobutyl)-benzene (57 mg, 40 %) as a slightly yellow oil, MS: m/e = 144.1 (M^+).

3-Phenyl-cyclobutanone is a known compound and has been prepared as described in the following reference: A. A. Frimer; J. Weiss; H. E. Gottlieb; J. L. Wolk; J. Org. Chem.; 59; 4; 1994; 780-792.

Example 129

3-Benzyl-cyclobutanone

A solution of (RS)-3-benzyl-2,2-dichlorocyclobutanone (0.3 g, 1.3 mmol) in acetic acid (3 ml) was refluxed for 1hour in the presence of zinc (0.86 g, 13.1 mmol, powder). The reaction mixture was cooled to room temperature and filtrated over decalite. The filtrate was neutralized with saturated $NaHCO_3$. The organic phase was washed successively with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 4:1) to provide 3-benzyl-cyclobutanone (0.16 g, 76 %) as a colorless oil, MS: m/e = 160.2 (M^+).

Example 130

(RS)-3-Benzyl-2,2-dichlorocyclobutanone

To a room temperature mixture containing allylbenzene (1.84 g, 15.6 mmol), zinc-copper couple (5.1g, 78 mmol) and diethylether (60 ml) was added dropwise a solution of trichloroacetylchloride (2.96 ml, 26.5 mmol) and phosphorus oxychloride (2.46 ml, 26.5 mmol) in diethylether (20 ml). The reaction mixture was stirred at room temperature for 1 hour, filtrated and the filtrate was partially concentrated. The residue was neutralized with saturated $NaHCO_3$. The aqueous phase was extracted with diethylether. The combined organic phases were washed successively with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (hexane) to provide (RS)-3-benzyl-2,2-dichlorocyclobutanone (0.71 g, 20 %) as a yellow oil, MS: m/e = 228.1 ($M-H^+$).

Example 131

Toluene-4-sulfonic acid 4-phenyl-but-3-ynyl ester

A mixture containing 3-butyn-1-ol 4-methylbenzenesulfonate (0.45 g, 2 mmol), iodobenzene (0.45 g, 2.2 mmol), CuI (0.038 g, 0.2 mmol), triethylamine (1.01 g, 10 mmol) and tetrakis(triphenylphosphine)palladium (0.12 g, 0.1 mmol) in toluene (10 ml) was stirred 30 minutes at room temperature, and 2 hours at 65 °C. The reaction mixture was cooled to room temperature, diluted with ethylacetate (10 ml), washed with H_2O (10 ml), dried over Na_2SO_4, and concentrated. The residue was chromatographed over silica gel (hexane-ethylacetate 9:1 then 4:1) to provide toluene-4-sulfonic acid 4-phenyl-but-3-ynyl ester (0.35 g, 58 %) as a brown oil, MS: m/e = 300 (M^+).

3-Butyn-1-ol 4-methylbenzenesulfonate is a known compound and has been prepared as described in the following reference: E. Bonfand; W. B. Motherwell; A. M. K. Pennell; M. K. Uddin; F. Ujjainwalla; Heterocycles; 46; 1997; 523-534.

Example 132

(2RS,3R)-2-Fluoro-1-[3-(4-hydroxy-phenylsulfanyl)-pyrrolidin-1-yl]-4-phenyl-butan-1-one

(RS)-2-Fluoro-4-phenyl-butyric acid (0.66 g, 3.63 mmol) was dissolved in DMF (5 ml) and carbonyldiimidazole (0.64 g, 3.8 mmol) was added portionwise. After evolution of CO_2 has ceased, the reaction mixture was warmed to 55 °C for 20 minutes and then cooled to room temperature. A mixture of triethylamine (0.46 ml, 3.3 mmol) and (3R)-4-(pyrrolidin-3-ylsulfanyl)-phenol trifluoroacetic acid (1.02 g, 3.3 mmol) in DMF (5 ml) was added. The mixture was stirred at room temperature for 2 hours.The solvent was removed in vacuo and the residue taken up in H_2O (30 ml).The mixture was extracted with ethylacetate (3 x 20 ml).The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was chromatographed over silica gel (CH_2Cl_2-MeOH, 99:1) to provide (2RS,3R)-2-fluoro-1-[3-(4-hydroxy-phenylsulfanyl)-pyrrolidin-1-yl]-4-phenyl-butan-1-one (1.12g, 95%) as light yellow oil, MS: m/e = 359.1(M^+).
The preparation of (3R)-4-(pyrrolidin-3-yl-sulfanyl)-phenol trifluoroacetic acid is described in example 90.

Following the general method of example 132 the compound of example 133 was prepared.

Example 133

(2RS,3S)-2-Fluoro-1-[3-(4-hydroxy-phenylsulfanyl)-pyrrolidin-1-yl]-4-phenyl-butan-1-one

The title compound, MS: m/e = 360.2 ($M+H^+$) was prepared from (RS)-2-fluoro-4-phenyl-butyric acid and (3S)-4-(pyrrolidin-3-yl-sulfanyl)-phenol hydrobromide.

Example 134

(3S)-4-[1-(2,2-Difluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol

To a –60 °C solution of oxalylchloride (0.21 ml, 2.42 mmol) in dry CH_2Cl_2 (4 ml) was added a solution of DMSO (0.34 ml, 4.84 mmol) in CH_2Cl_2 (2 ml). After 5 minutes stirring, a solution of 2,2-difluoro-4-phenyl-butan-1-ol (0.41 g, 2.2 mmol) in CH_2Cl_2 was added dropwise at –60 °C. After 15 minutes stirring, triethylamine (1.54 ml, 11 mmol) was added dropwise, the reaction mixture was allowed to warm up to room temperature and H_2O (10 ml) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml).The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was dissolved in 1,2-dichloroethane (15 ml) and added to a suspension of (3S)-4-(pyrrolidin-3-ylsulfanyl)-phenol hydrobromide (0.68 g, 2.2 mmol), triethylamine (0.31 ml, 2.2 mmol) and sodium triacetoxyborohydride (0.74 g, 3.30 mmol) in 1,2-dichloroethane (45 ml). Mixture was stirred at 65 °C for 2 hours and overnight at room temperature. H_2O (30 ml) was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml).The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was chromatographed over silica gel (hexane-ethylacetate 99:1 to 90:10) to provide (3S)-4-[1-(2,2-difluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol (0.55g, 70%) as light yellow oil, MS: m/e = 364.2($M+H^+$).

Following the general method of example 134, the compound of example 135 was prepared.

Example 135

(3R)-4-[1-(2,2-Difluoro-4-phenyl-butyl)-pyrrolidin-3-ylsulfanyl]-phenol

The title compound, MS: m/e = 364.2 ($M+H^+$) was prepared from 2,2-difluoro-4-phenyl-butan-1-ol and (3R)-4-(pyrrolidin-3-ylsulfanyl)-phenol trifluoroacetic acid.

Example 136

(RS)-2-Fluoro-4-phenyl-butyric acid

(RS)-2-Fluoro-4-phenyl-butyric acid methyl ester (0.39 g, 2 mmol) was added to a solution of KOH (0.56 g, 10 mmol) in EtOH (5 ml). After 1 hour stirring at room temperature, the reaction mixture was concentrated, diluted with H_2O (5 ml), acidified to pH 1 with 2N HCl and extracted with CH_2Cl_2 (3 times). The combined organic phases were dried over Na_2SO_4, filtered and concentrated to provide (RS)-2-fluoro-4-phenyl-butyric acid (0.343 g, 92 %) as a colorless oil MS: m/e = 182.1 (M^+).

The preparation of (RS)-2-fluoro-4-phenyl-butyric acid methyl ester is described example 122.

Example 137

2,2-Difluoro-4-phenyl-butan-1-ol

2,2-Difluoro-4-phenyl-butyric acid ethyl ester (0.23 g, 1 mmol) was dissolved in EtOH (4 ml) and treated with $NaBH_4$ (39.4 mg, 1 mmol). After 30 minutes stirring at room temperature, the reaction mixture was cooled to 0 °C, acidified to pH 1 with 1N HCl (2 ml), diluted with H_2O (10 ml). The aqueous phase was extracted with ether (3 times). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was chromatographed over silica gel (hexane-ethylacetate 99:1) to provide 2,2-difluoro-4-phenyl-butan-1-ol (0.11 g, 58%) as light yellow oil, MS: m/e = 186.1 (M^+).

Example 138

2,2-Difluoro-4-phenyl-butyric acid ethyl ester

Ethyl 2-oxo-4-phenylbutyrate (1 g, 4.7 mmol) was treated with (diethylamino)sulfur trifluoride (1.3 ml, 9.4 mmol). After 2 hours stirring at room temperature, the reaction mixture was poured on H_2O-ice. The aqueous phase was extracted with CH_2Cl_2 (2 times). The combined organic phases were washed with H_2O, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was distilled to provide 2,2-difluoro-4-phenyl-butyric acid ethyl ester (1.0 g, 94 %) as yellow oil, MS: m/e = 228.1 (M^+), b.p.: 90°C, 0.2 mbar.

Ethyl 2-oxo-4-phenylbutyrate is a commercially available compound.

Example A

Tablet Formulation (Wet Granulation)

Item	Ingredients	mg/tablet			
1.	Compound of formula 1	5	25	100	500
2.	Lactose Anhydrous DTG	125	105	30	150
3.	Sta-Rx 1500	6	6	6	30
4.	Microcrystalline Cellulose	30	30	30	150
5.	Magnesium Stearate	1	1	1	1
	Total	167	167	167	831

Manufacturing Procedure

1 Mix items 1, 2, 3 and 4 and granulate with purified water.
2. Dry the granulation at 50°C.
3. Pass the granulation through suitable milling equipment.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Example B

Capsule Formulation

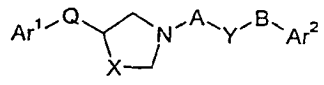
Item Ingredients	mg/tablet			
1. Compound of formula 1	5	25	100	500
2. Hydrous Lactose	159	123	148	---
3. Corn Starch	25	35	40	70
4. Talc	10	15	10	25
5. Magnesium Stearate	1	2	2	5
Total	200	200	300	600

Manufacturing Procedure

1 Mix items 1, 2, and 3 in a suitable mixer for 30 minutes.
2. Add items 4 and 5 and mix for 3 minutes.
3. Fill into a suitable capsule.
4. Add item 5 and mix for three minutes; compress on a suitable press.

Claims

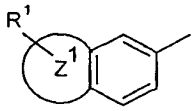
1. Compounds of formula



I

wherein

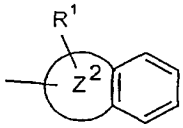
Ar^1 is pyridyl or phenyl, substituted by hydroxy, lower alkyl, halogen, amino, nitro, benzyloxy or lower alkoxy-lower alkoxy, or is the group



wherein Z^1 is a five membered heterocyclic ring, which contains one or two heteroatoms, selected from N or O;

R^1 is hydrogen, hydroxy or an oxo group;

Ar^2 is pyridyl or phenyl, optionally substituted by hydroxy, lower alkyl, halogen, amino, nitro, benzyloxy or lower alkoxy-lower alkoxy, or is the group



wherein Z^2 is a five or six membered ring, which optionally contains one or two heteroatoms, selected from N or O; and

Q is –S-, -S(O)- or $-S(O)_2-$;

X is a bond, -CH(OH)- or $-(CH_2)_n-$;

A is a bond or $-(CHR)_m-$;

R is hydrogen, halogen or hydroxy, independently from each other if m is 2 or 3;

Y is $-(CR_2)_m-$, -O-, -C=C-, -C≡C-, piperidin-1-yl, pyrrolidin-1-yl or C_4-C_6-cycloalkyl, which rings are optionally substituted by hydroxy;

B is a bond, -O- or $-(CHR)_m$;

n is 1 or 2; and

m is 1, 2 or 3;

and pharmaceutically acceptable acid addition salts thereof with the exception of compounds, wherein A and B are simultaneously a bond and Y is –CHR-.

2. Compounds according to claim 1, wherein Ar^1 is phenyl, substituted by hydroxy, Q is –S-, Ar^2 is phenyl and X is $–CH_2$-.

3. Compounds according to claim 2, which are

(S)-4-[1-(4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(RS)-4-[1-(4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(R)-4-[1-(4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(2R, 3S) or (2S, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(2S, 3S) or (2R, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(RS)-4-[1-(3-phenyl-propyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(3RS, 3RS) and (3RS, 3SR)-4-[1-(3-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(2S, 3R) or (2R, 3R)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol,
(2RS,3S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol or
(2RS,3R)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidin-3-yl-sulfanyl]-phenol.

4. Compounds according to claim 1, wherein Ar^1 is phenyl, substituted by hydroxy, Q is –S(O)-, Ar^2 is phenyl and X is $–CH_2$.

5. A compound according to claim 4, which is

(3RS, S-oxide RS) and (3RS, S-oxide SR)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol,
(2R,3R, S-oxide R)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol,
(2S,3S, S-oxide R)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol,
(2R,3S, S-oxide R)-4-[1-(2-fuoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol or
(3S, S-oxide S) or (3S, S-oxide R)-4-[1-(2,2-difluoro-4-phenyl-butyl)-pyrrolidine-3-sulfinyl]-phenol.

6. Compounds according to claim 1, wherein Ar^1 is phenyl, substituted by hydroxy, Q is $–S(O)_2$-, Ar^2 is indanyl or phenyl, optionally substituted by methyl and X is $–CH_2$- or –CH(OH)-.

7. Compounds according to claim 6, which are

(S)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(RS)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,

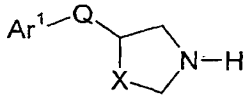
(2R, 3S) and (2S, 3S)-4-[1-(2-fluoro-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(3RS, cis) and (3RS, trans)-4-[1-(3-benzyl-cyclobutyl)-pyrrolidine-3-sulfonyl]-phenol,
(3RS, cis)- 4-[1-(4-phenyl-cyclohexyl)-pyrrolidine-3-sulfonyl]-phenol,
(3RS,4RS)-4-(4-hydroxy-benzenesulfonyl)-1-(4-phenyl-butyl)-pyrrolidin-3-ol,
(RS)-4-[1-(4-m-tolyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(RS)-4-[1-(3-phenyl-propyl)-pyrrolidine-3-sulfonyl]-phenol,
(R)-4-[1-(4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol,
(RS)-4-[1-(1-phenyl-piperidin-4-yl)-pyrrolidine-3-sulfonyl]-phenol or
(2R, 3S) or (2S, 3S)-4-[1-(2-hydroxy-4-phenyl-butyl)-pyrrolidine-3-sulfonyl]-phenol.

8. A medicament containing one or more compounds of any one of claims 1 to 7 or a pharmaceutically acceptable salt thereof and an inert carrier for the treatment of diseases.

9. A medicament according to claim 8 for the treatment of diseases based on therapeutic indications for NMDA receptor subtype specific blockers, which include acute forms of neurodegeneration caused, e.g., by stroke and brain trauma, and chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis) and neurodegeneration associated with bacterial sclerosis) and neurodegeneration associated with bacterial or viral infections.

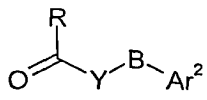
10. A process for preparing a compound of formula I as defined in claim 1, which process comprises

a) reacting a secondary amine of formula



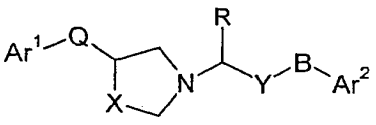
II

with an aldehyde or ketone of formula



III

to a compound of formula

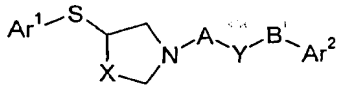


I-1

wherein Ar^1, Ar^2, Q, X, Y, R and B have the significances given above,

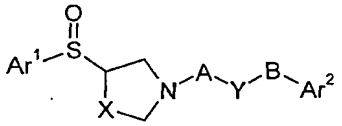
or

b) oxydizing a compound of formula



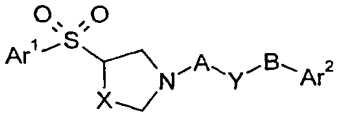
I-2

to a compound of formula



I-3

and /or to a compound of formula

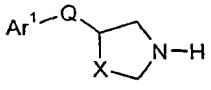


I-4

wherein Ar^1, Ar^2, X, A, Y and B have the significances given above,

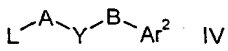
or

c) reacting a secondary amine of formula



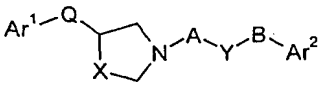
II

with a compound of formula



IV

to give a compound of formula

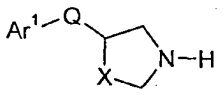


I

wherein L is a leaving group, such as Cl, Br or p-toluenesulfonate and Ar^1, Ar^2, Q, X, A, Y and B have the significances given above,

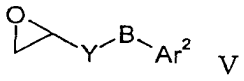
or

d) reacting a secondary amine of formula



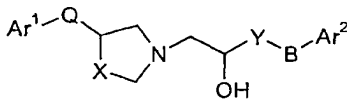
II

with a compound of formula



V

to give a compound of formula

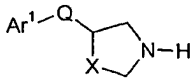


I-5

wherein Ar^1, Ar^2, Q, X, Y and B have the significances given above,

or

e) reacting a secondary amine of formula

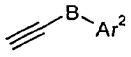


II

with an aldehyde of formula

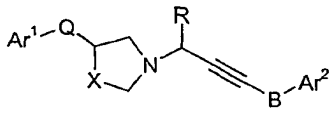
VI

and with an alkyne of formula



VII

to give a compound of formula

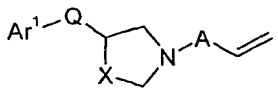


I-6

wherein Ar^1, Ar^2, Q, X, R and B have the significances given above ,

or

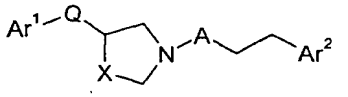
f) reacting a compound of formula


VIII

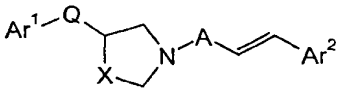
with a compound of formula

Ar^2hal

to give a comound of formula


I-7

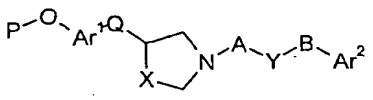
or


I-8

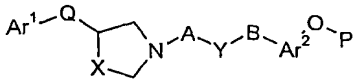
wherein Ar^1, Ar^2, Q, X and A have the significances given above ,

or

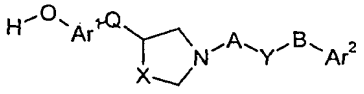
g) cleaving off a O-protecting group of compounds of formula


X

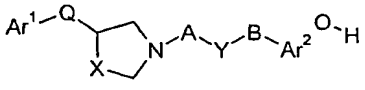
or


XI

to obtain a compound of formula


I-9

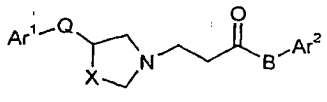
or


I-10

wherein Ar^1, Ar^2, Q, X, A, Y and B have the significances given above and P is a O-protecting group, for example benzyl or a methoxymethyl group,

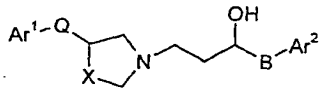
or

h) reducing a compound of formula



XII

to a compound of formula

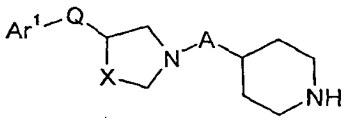


I-11

wherein Ar^1, Ar^2, Q, X and B have the significances given above;

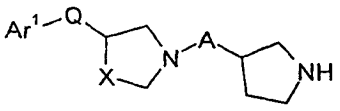
or

i) reacting a compound of formula



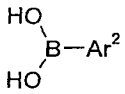
XIV-2

or



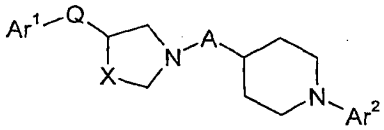
XIV-1

with a compound of formula



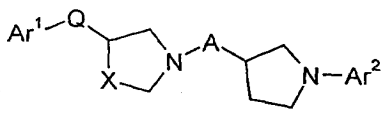
XV

to obtain a compound of formula



I-13

or



I-12

wherein Ar^1, Ar^2, Q, X, A and B have the significances given above;

and

if desired, modifying one or more substituents within the definitions given above, or if desired, converting the compound of formula I obtained into a pharmaceutically acceptable salt.

11. A compound according to any one of claims 1-7 whenever prepared by a process as claimed in claim 10 or by an equivalent method.

12. The use of a compound in accordance with any one of claims 1 - 7 for the treatment of diseases.

13. The use of a compound in accordance with claims 1 - 7 for the manufacture of a medicament for the treatment of diseases, based on therapeutic indications for NMDA receptor subtype specific blockers, which include acute forms of neurodegeneration caused e.g, by stroke and brain trauma, and chronic forms of neurodegeneration such as Alzheimer's disease, Parkinson's disease, Huntington's disease, ALS (amyotrophic lateral sclerosis) and neurodegeneration associated with bacterial or viral infections, and chronic or acute pain.

14. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/04171

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D207/12 C07D211/54 C07D231/56 C07D263/58 C07D209/34
C07D205/04 A61K31/40 A61K31/44 A61K31/395 A61P25/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 937 458 A (F. HOFFMANN-LA ROCHE) 25 August 1999 (1999-08-25) page 2, line 35 - line 53; claims; examples	1-14
Y	WO 97 23215 A (WARNER-LAMBERT) 3 July 1997 (1997-07-03) page 30, line 22 -page 32, line 12; claims; examples	1-14
P,Y	WO 00 75109 A (F. HOFFMANN-LA ROCHE) 14 December 2000 (2000-12-14) page 2, line 6 - line 23; claims; examples	1-14
A	EP 0 160 436 A (A.H. ROBINS CO.) 6 November 1985 (1985-11-06) cited in the application claims; examples	1-14

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 August 2001	20/08/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Helps, I

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/04171

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	A. PADWA ET. AL.: "On the Use of N-'(Trimethylsilyl)methyl!amino Ethers as Capped Azomethine Ylide Equivalents." JOURNAL OF ORGANIC CHEMISTRY, vol. 52, no. 2, 1987, pages 235-44, XP000601501 page 235, compound no. 6	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 01/04171

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 937458 A	25-08-1999	AU 1635499 A	26-08-1999
		BR 9900742 A	09-05-2000
		CN 1232025 A	20-10-1999
		CZ 9900410 A	15-09-1999
		HR 990042 A	29-02-2000
		HU 9900275 A	28-12-1999
		JP 3142527 B	07-03-2001
		JP 2000063384 A	29-02-2000
		NO 990609 A	11-08-1999
		PL 331336 A	16-08-1999
		SG 74120 A	18-07-2000
		TR 9900286 A	21-09-1999
		US 6015824 A	18-01-2000
		US 6153624 A	28-11-2000
WO 9723215 A	03-07-1997	AU 1354597 A	17-07-1997
		US 6124317 A	26-09-2000
		ZA 9610736 A	27-06-1997
WO 0075109 A	14-12-2000	AU 5218100 A	28-12-2000
EP 160436 A	06-11-1985	AU 565886 B	01-10-1987
		AU 3811685 A	17-10-1985
		CA 1247093 A,C	20-12-1988
		CA 1256866 A	04-07-1989
		IL 74140 A	31-05-1988
		JP 60228454 A	13-11-1985
		PH 22414 A	26-08-1988
		PH 22573 A	17-10-1988
		US 4593102 A	03-06-1986
		US 4642348 A	10-02-1987